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(54) Title: GENES AND PROTEINS FOR PREVENTION, PREDICTION, PROGNOSIS AND THERAPY OF CARDIOVASCULAR DISEASE

(57) Abstract: Genes that are differentially expressed in blood vessels of cardiovascular disease patients versus blood vessels of normal people are disclosed. The genes provide novel methods, uses and compositions for the prediction, prevention, diagnosis, prognosis and treatment of cardiovascular disease.

**GENES AND PROTEINS FOR PREVENTION, PREDICTION, PROGNOSIS
AND THERAPY OF CARDIOVASCULAR DISEASE**

TECHNICAL FIELD OF THE INVENTION

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The present invention relates to polynucleotide sequences and polypeptides thereof for the diagnosis and treatment of cardiovascular disease, including, but not limited to, arteriosclerosis, angina pectoris, myocardial infarction, ischemia, restenosis, and arterial inflammation. Specifically, the present invention identifies and describes
10 genes which are differentially expressed in cardiovascular disease states, relative to their expression in normal, and/or in response to manipulations relevant to cardiovascular disease (e.g. incubation of isolated macrophages in the presence of enzymatic modified LDL). In particular genes that are up- or down-regulated in macrophages of patients with inherited predisposition for arteriosclerosis are
15 disclosed. Also disclosed are methods for utilizing such genes, polynucleotides or polypeptides derived from the genes as diagnostic markers for cardiovascular disease, particularly arteriosclerosis.

Still further, the present invention provides methods for the identification and
20 therapeutic use of antibodies for treatment of cardiovascular disease. Moreover, the present invention provides methods for the diagnostic monitoring of patients undergoing clinical evaluation for the treatment of cardiovascular disease, and for monitoring the efficacy of compounds in clinical trials. Additionally, the present invention describes methods for the diagnostic evaluation and prognosis of various
25 cardiovascular diseases, and for the identification of subjects exhibiting a predisposition to such conditions

Methods of screening for activators and inhibitors which can be used for the regulation of polypeptides derived from the genes and therapeutic uses of these
30 modulators are also disclosed.

BACKGROUND OF THE INVENTION

Cardiovascular diseases such as arteriosclerosis, ischemia, myocardial infarction, and angina pectoris are a major health risk throughout the industrialized world.

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Arteriosclerosis

The principal cell types of the artery wall, the endothelial cell, the smooth muscle cell and the monocyte/macrophage, are major players in the events involved in initiation and evolution of the arteriosclerotic plaque. The process, in normal circumstances a protective response to insults to the endothelium and smooth muscle cells (SMCs) of the wall of the artery, consists of the formation of fibrofatty and fibrous lesions (fatty streaks) or plaques, preceded and accompanied by inflammation.

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The first observable event in the formation of an arteriosclerotic plaque occurs when blood-borne monocytes adhere to the vascular endothelial layer and transmigrate through to the sub-endothelial space. Within the vessel wall monocytes differentiate into macrophages due to the extracellular stimuli. Adjacent endothelial cells at the same time produce oxidized low density lipoprotein (LDL). These oxidized LDL's are then taken up in large amounts by the macrophages through scavenger receptors expressed on their surfaces. In contrast to the tightly regulated pathway by which native LDL (nLDL) is taken up by nLDL specific receptors. But not only genes of the LDL uptake machinery are of great diagnostic and therapeutic interest since the cellular cholesterol content is normally under strict homeostatic control, and mechanisms of *de novo* synthesis and efflux are also highly regulated. Cholesterol efflux pathways have been a focus of much recent attention, as studies on protein and cholesterol transport converged, pointing at cholesterol-rich membrane microdomains or proteolipid complexes, or both, as carriers of newly synthesised free cholesterol to the plasma membrane. Cellular cholesterol is accrued by:

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- (i) internalisation of intact low-density lipoprotein (LDL) carrying cholesteryl-ester by endocytosis via high-affinity LDL receptors;
- (ii) selective uptake of free cholesterol by monomer exchange, mainly from LDL;
- (iii) selective uptake of cholesteryl ester by exchange, mainly from HDL; and
- (iv) *de novo* synthesis of cholesterol by the mevalonate pathway in the endoplasmic reticulum (ER).

Several lines of evidence suggest that the pathways involved in transport of protein and cholesterol from the ER to the plasma membrane are different. In arteriosclerosis either of these pathways is disturbed and as a consequence lipid-filled macrophages, so called foam cells, and their accumulation lead to the development of fatty streaks. Some fatty streaks subsequently accumulate smooth muscle cells, which migrate from the medial layer. With the secretion of extracellular matrix molecules by the smooth muscle cells, fibrous plaques develop and increase in size. Progression of the disease is characterised by the accumulation of lipids and fibrous elements in the large arteries. The advanced lesions of arteriosclerosis may occlude the artery concerned, and result from an excessive inflammatory-fibroproliferative response to numerous different forms of insult, resulting in restriction of the flow of blood, leading to ischemia. For example, shear stresses are thought to be responsible for the frequent occurrence of arteriosclerotic plaques in regions of the circulatory system where turbulent blood flow occurs, such as branch points and irregular structures [for review see Lusis et al., (2)].

Especially the anterior descending branch of the left coronary artery is susceptible to arteriosclerosis. With time, these plaques can lead to a partial reduction or a sudden total block of the blood's flow. In rare cases coronary artery spasm of unknown origin can provoke that situation as well. The major complications are angina pectoris, myocardial infarction, and sudden cardiac death.

Ischemia

Ischemia is a sequela of arteriosclerosis characterised by a lack of oxygen supply in tissues of organs due to inadequate perfusion. Such inadequate perfusion can have
5 number of natural causes, including arterioosclerotic or restenotic lesions, anaemia, or stroke, to name a few. Many medical interventions, such as the interruption of the flow of blood during bypass surgery, for example, also lead to ischemia. In addition to sometimes being caused by diseased cardiovascular tissue, ischemia may sometimes affect cardiovascular tissue, such as in ischemic heart disease. Ischemia
10 may occur in any organ, however, that is suffering a lack of oxygen supply. Not infrequently, two or more causes of ischemia will coexist, such as an increase in oxygen demand due to left ventricular hypertrophy and a reduction in oxygen supply secondary to coronary arteriosclerosis.

15 Angina pectoris

Angina pectoris, another sequela of arteriosclerosis, is characterised by episodes of chest discomfort and pressure due to insufficient blood supply, typically precipitated by exertion and relieved by rest. Angina pectoris is usually triggered by activity, emotional stress, or temperatures and persists only a few minutes. The blood
20 circulation and oxygen supply of the cardiac muscle is reduced for a short period of time due to constriction of coronary arteries.

With progressive arteriosclerosis sensations of pain can be experienced even during periods of rest. Angina pectoris certainly is a sign that a person is at increased risk of
25 heart attack.

Myocardial infarction

A heart attack or myocardial infarction occurs when the supply of oxygen and
30 nutrient-rich blood to the heart muscle is severely reduced or cut off completely, resulting in sharp pain. In most patients an acute thrombus, often associated with

plaque rupture, occludes the artery. If the blood supply is shut down for a long time cardiac muscle cells die from lack of oxygen. If only a small part of the heart muscle is deprived of oxygen the victim might recover. However, disability or death can result, depending on how much the heart muscle is damaged. Therefore, people with
5 a genetic predisposition or risk factors like diabetes, hypertension, high cholesterol, and obesity should be extremely careful.

Early diagnosis of patients at risk to develop arteriosclerosis will allow to initiate early preventative steps. Prevention, optimal treatment, and rehabilitation measures
10 are necessary to avoid the sequela of arteriosclerosis such as stroke, angina pectoris, ischemia, or myocardial infarction, to improve the quality of life and to extend overall survival in these patients.

Arteriosclerosis, the most prevalent cardiovascular disease, is the principal cause of
15 heart attack, stroke, and gangrene of the extremities, and thereby the principle cause of death in the United States. Arteriosclerosis is now recognized as a multifactorial disease process associated with several important environmental and genetic risk factors [for a detailed review, see Ross et al. (1)]. Such risk factors include hypertension, elevated levels of homocysteine or LDL/VLDL, smoking, diabetes mellitus,
20 and obesity. Because of the presumed role of the excessive inflammatory-fibroproliferative response in arteriosclerosis and ischemia, a number of researchers have investigated, in the context of arterial injury, the expression of certain factors involved in inflammation, cell recruitment and proliferation. These factors include growth factors, cytokines, and other chemicals, including lipids involved in cell
25 recruitment and migration, cell proliferation and the control of lipid and protein synthesis. These results so far have not lead to satisfactory improvements for the patients and subsequently there is an ongoing need for novel preventive, predictive, diagnostic, prognostic and therapeutic compositions, uses and methods. The foregoing studies are aimed at defining the role of particular gene products in the
30 excessive inflammatory-fibroproliferative response leading to arteriosclerotic plaque formation.

SUMMARY OF THE INVENTION

5 The present invention relates to novel preventive, predictive, diagnostic, prognostic and therapeutic compositions, uses and methods for cardiovascular diseases and arteriosclerosis in particular. Specifically, 74 genes are identified and described which are differentially expressed in cardiovascular disease states, relative to their expression in normal, or non-cardiovascular disease states, as well as derivatives, fragments, analogues and homologues thereof. Especially membrane bound marker
10 gene products containing extracellular domains can be a particularly useful target for treatment methods as well as diagnostic and clinical monitoring methods.

The invention is based, in part, on systematic search strategies involving *in vivo* and
15 *in vitro* cardiovascular disease experiments coupled with sensitive and high throughput gene expression assays, based on DNA chip technology. In contrast to approaches that merely evaluate the expression of a given gene product presumed to play a role in a disease process, the search strategies and assays used herein permit the identification of all genes, whether known or novel, that are expressed or repressed in the disease condition, as well as the evaluation of their temporal
20 regulation and function during disease progression. This comprehensive approach and evaluation permits the discovery of novel genes and gene products, as well as the identification of an array of genes and gene products (whether novel or known) involved in novel pathways that play a major role in the disease pathology. Thus based on the identification of genes relevant for the pathophysiology of
25 cardiovascular diseases such as arteriosclerosis and its sequela, the invention provides novel targets useful for prevention, prediction, diagnosis, prognosis monitoring, rational drug screening and design, and/or other therapeutic intervention of cardiovascular diseases and arteriosclerosis in particular.

30 "Differential expression", as used herein, refers to both quantitative as well as qualitative differences in the genes' expression patterns depending on differential

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development and/or reaction to lipid environment of macrophages. Differentially expressed genes may represent "marker genes," and/or "target genes" which are named "CVD genes" or "CVD gene" hereinafter. "CVD genes" or "CVD gene" refers to polynucleotides but also to the polypeptides encoded thereby. The expression pattern of a differentially expressed "CVD gene" may be utilized as part of a prognostic or diagnostic cardiovascular disease evaluation., Alternatively, a "CVD gene" may be used in methods for identifying reagents and compounds and uses of these reagents and compounds for the treatment of cardiovascular disease as well as methods of treatment. Also "CVD gene" refers to a differentially expressed gene involved in cardiovascular diseases such that modulation of the level of target gene expression or of target gene product activity may act to ameliorate a cardiovascular disease condition. Compounds that modulate target gene expression or activity of the target gene product can be used in the treatment of cardiovascular disease.

It is an objective of the invention to provide methods and reagents for the prediction, prevention, diagnosis, prognosis and therapy of cardiovascular disease and in particular arteriosclerosis.

In one embodiment, the invention pertains to a method of determining the phenotype of a cell or tissue, comprising detecting the differential expression, relative to a normal or untreated cell, of at least one nucleic acid comprising SEQ ID Nos. 1 to 74, wherein the nucleic acid is differentially expressed by at least about 1.5 fold, at least about 2 fold, at least about 3 fold.

In a further aspect the invention pertains to a method of determining the phenotype of a cell or tissue, comprising detecting the differential expression, relative to a normal or untreated cell, of at least one nucleic acid which hybridises under stringent conditions to one of SEQ ID Nos. 1 to 74, wherein the nucleic acid is differentially expressed by at least at least about 1.5 fold , at least about 2 fold or at least about 3 fold.

In another embodiment of the invention a "CVD gene" or a gene product of a "CVD gene" can be used to identify cells or tissue in individuals which exhibit a phenotype predisposed to cardiovascular disease or a diseased phenotype, thereby (a) predicting whether an individual is at risk for the development, or (b) diagnosing whether an individual is having, or (c) prognosing the progression or the outcome of the treatment cardiovascular disease and arteriosclerosis in particular.

In yet another embodiment the invention provides methods of screening for agents which regulate the activity of a polypeptide encoded by a "CVD gene". A test compound is contacted with a polypeptide encoded by a "CVD gene". Binding of the test compound to the polypeptide is detected. A test compound which binds to the polypeptide is thereby identified as a potential therapeutic agent for the treatment of cardiovascular disease and more particularly arteriosclerosis.

In even another embodiment the invention provides another method of screening for agents which regulate the activity of a polypeptide encoded by a "CVD gene". A test compound is contacted with a polypeptide encoded by a "CVD gene". A biological activity mediated by the polypeptide is detected. A test compound which decreases the biological activity is thereby identified as a potential therapeutic agent for decreasing the activity of the polypeptide encoded by a "CVD gene" in cardiovascular disease and arteriosclerosis in particular. A test compound which increases the biological activity is thereby identified as a potential therapeutic agent for increasing the activity of the polypeptide encoded by a "CVD gene" in cardiovascular disease and arteriosclerosis in particular.

In another embodiment the invention provides a method of screening for agents which regulate the activity of a "CVD gene". A test compound is contacted with a "CVD gene" polynucleotide. Binding of the test compound to the "CVD gene" polynucleotide is detected. A test compound which binds to the polynucleotide is thereby identified as a potential therapeutic agent for regulating the activity of the "CVD gene" in cardiovascular disease and arteriosclerosis in particular.

The invention thus provides "CVD genes" which can be used to identify compounds which may act, for example, as regulators or modulators such as agonists and antagonists, partial agonists, inverse agonists, activators, co-activators and inhibitors of the polypeptide encoded by a "CVD gene". Accordingly, the invention provides reagents and methods for regulating a "CVD gene" polynucleotide or a polypeptide encoded by a "CVD gene" in cardiovascular disease and more particularly arteriosclerosis. The regulation can be an up- or down regulation. Reagents that modulate the expression, stability or amount of a "CVD gene" polynucleotide or the activity of the polypeptide encoded by a "CVD gene" can be a protein, a peptide, a peptidomimetic, a nucleic acid, a nucleic acid analogue (e.g. peptide nucleic acid, locked nucleic acid) or a small molecule.. Methods that modulate the expression, stability or amount of a "CVD gene" polynucleotide or the activity of the polypeptide encoded by a "CVD gene" can be gene replacement therapies, antisense, ribozyme and triplex nucleic acid approaches.

In one embodiment of the invention provides antibodies which specifically bind to a full-length or partial "CVD gene" polynucleotide or a polypeptide for use in prediction, prevention, diagnosis, prognosis and treatment of cardiovascular disease.

Yet another embodiment of the invention is the use of a reagent which specifically binds to a "CVD gene" polynucleotide or a polypeptide encoded by a "CVD gene" in the preparation of a medicament for the treatment of cardiovascular disease and arteriosclerosis in particular.

Still another embodiment is the use of a reagent that modulates the activity or stability of a "CVD gene" polypeptide or the expression, amount or stability of a "CVD gene" mRNA in the preparation of a medicament for the treatment of cardiovascular disease and arteriosclerosis in particular.

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Still another embodiment of the invention is a pharmaceutical composition which includes a reagent which specifically binds to a "CVD gene" polynucleotide or a polypeptide encoded by a "CVD gene", and a pharmaceutically acceptable carrier.

- 5 Yet another embodiment of the invention is a pharmaceutical composition including the subject nucleic acids. In one embodiment, a reagent which alters the level of expression in a cell of a nucleic acid comprising one of SEQ ID Nos. 1 to 74, or a sequence complementary thereto, is identified by providing a cell, treating the cell with a test reagent, determining the level of expression in the cell of a nucleic acid of
10 SEQ ID Nos. 1 to 74 or a sequence complementary thereto, and comparing the level of expression of the nucleic acid in the treated cell with the level of expression of the nucleic acid in an untreated cell, wherein a change in the level of expression of the nucleic acid in the treated cell relative to the level of expression of the nucleic acid in the untreated cell is indicative of an agent which alters the level of expression of the
15 nucleic acid in a cell. The invention further provides a pharmaceutical composition comprising a reagent identified by this method.

- Another embodiment of the invention is a pharmaceutical composition which includes a polypeptide either encoded by a nucleic acid having a nucleotide sequence
20 comprising one of SEQ ID Nos. 1 to 74 or a sequence complementary thereto, or having the sequence of SEQ ID Nos. 75 to 147. In one embodiment, the invention pertains to a pharmaceutical composition comprising a nucleic acid including a sequence which hybridises under stringent conditions to one of SEQ ID Nos. 1 to 74 or a sequence complementary thereto. Pharmaceutical compositions, useful in the
25 present invention may further include fusion proteins comprising the amino acid sequence of SEQ ID Nos. 75 to 147, or a fragment thereof, antibodies, or antibody fragments

DETAILED DESCRIPTION OF THE INVENTION

Definitions

5 “Biological activity” or “bioactivity” or “activity” or “biological function”, which are used interchangeably, herein mean an effector or antigenic function that is directly or indirectly performed by a polypeptide (whether in its native or denatured conformation), or by any fragment thereof *in vivo* or *in vitro*. Biological activities include but are not limited to binding to polypeptides, binding to other proteins or molecules, enzymatic activity, signal transduction, activity as a DNA binding
10 protein, as a transcription regulator, ability to bind damaged DNA, etc. A bioactivity can be modulated by directly affecting the subject polypeptide. Alternatively, a bioactivity can be altered by modulating the level of the polypeptide, such as by modulating expression of the corresponding gene.

15 The term “biomarker” refers a biological molecule, e.g., a nucleic acid, peptide, hormone, etc., whose presence or concentration can be detected and correlated with a known condition, such as a disease state.

The term “biological sample”, as used herein, refers to a sample obtained from an
20 organism or from components (e.g., cells) of an organism. The sample may be of any biological tissue or fluid. Frequently the sample will be a “clinical sample” which is a sample derived from a patient. Such samples include, but are not limited to, sputum, blood, blood cells (e.g., white cells), tissue or fine needle biopsy samples, urine, peritoneal fluid, and pleural fluid, or cells therefrom. Biological samples may
25 also include sections of tissues such as frozen sections taken for histological purposes.

By “array” or “matrix” is meant an arrangement of addressable locations or
30 “addresses” on a device. The locations can be arranged in two dimensional arrays, three dimensional arrays, or other matrix formats. The number of locations can range from several to at least hundreds of thousands. Most importantly, each location

represents a totally independent reaction site. Arrays include but are not limited to nucleic acid arrays, protein arrays and antibody arrays. A "nucleic acid array" refers to an array containing nucleic acid probes, such as oligonucleotides or larger portions of genes. The nucleic acid on the array is preferably single stranded. Arrays wherein the probes are oligonucleotides are referred to as "oligonucleotide arrays" or "oligonucleotide chips." A "microarray," also referred to herein as a "biochip" or "biological chip" is an array of regions having a density of discrete regions of at least about 100/cm², and preferably at least about 1000/cm². The regions in a microarray have typical dimensions, e.g., diameters, in the range of between about 10-250 μ m, and are separated from other regions in the array by about the same distance. A "protein array" refers to an array containing polypeptide probes or protein probes which can be in native form or denatured. An "antibody array" refers to an array containing antibodies which include but are not limited to monoclonal antibodies (e.g. from a mouse), chimeric antibodies, humanized antibodies or phage antibodies and single chain antibodies as well as fragments from antibodies.

"Small molecule" as used herein, is meant to refer to a composition, which has a molecular weight of less than about 5 kD and most preferably less than about 4 kD. Small molecules can be nucleic acids, peptides, polypeptides, peptidomimetics, carbohydrates, lipids or other organic (carbon-containing) or inorganic molecules. Many pharmaceutical companies have extensive libraries of chemical and/or biological mixtures, often fungal, bacterial, or algal extracts, which can be screened with any of the assays of the invention to identify compounds that modulate a bioactivity.

"Marker gene," as used herein, refers to a differentially expressed gene whose expression pattern may be utilized as part of a prognostic or diagnostic cardiovascular disease evaluation, or which, alternatively, may be used in methods for identifying compounds useful for the treatment of cardiovascular disease. A marker gene may also have the characteristics of a target gene.

"Target gene", as used herein, refers to a differentially expressed gene involved in cardiovascular disease in a manner by which modulation of the level of target gene expression or of target gene product activity may act to ameliorate symptoms of cardiovascular disease. A target gene may also have the characteristics of a marker gene.

The terms "modulated" or "modulation" and "differentially regulated" as used herein refer to both upregulation (i.e., activation or stimulation (e.g., by agonizing or potentiating) and down regulation [i.e., inhibition or suppression (e.g., by antagonizing, decreasing or inhibiting)].

"Transcriptional regulatory unit" refers to DNA sequences, such as initiation signals, enhancers, and promoters, which induce or control transcription of protein coding sequences with which they are operably linked. In preferred embodiments, transcription of one of the genes is under the control of a promoter sequence (or other transcriptional regulatory sequence) which controls the expression of the recombinant gene in a cell-type in which expression is intended. It will also be understood that the recombinant gene can be under the control of transcriptional regulatory sequences which are the same or which are different from those sequences which control transcription of the naturally occurring forms of the polypeptide.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

The present invention provides nucleic acid sequences and proteins encoded thereby, as well as probes derived from the nucleic acid sequences, antibodies directed to the encoded proteins, and predictive, preventive, diagnostic, prognostic and therapeutic methods for individuals which are at risk for or which have cardiovascular disease and arteriosclerosis in particular. The sequences disclosure herein have been found to be differentially expressed in samples relevant for cardiovascular diseases.

The present invention is based on the identification of 74 genes that are differentially regulated (up- or downregulated) in macrophages with/without incubation with eLDL of patients with clinical evidence of CVD. The identification of 74 human genes which were not known to be differentially regulated in cardiovascular disease states and their significance for the disease is described in the working examples herein. The characterisation of the expression of these genes in particular disease states provides newly identified roles in cardiovascular diseases. The gene names, the database accession numbers (GenBank and UniGene) and the fold-regulation values are given in the Tables 1 and 2. The primer sequences used for the gene amplification are shown in Table 3. Table 4 provides information about the gene function the functional class of the proteins which are encoded by the 74 differentially regulated genes.

In either situation, detecting expression of these genes in excess of normal expression provides for the diagnosis of cardiovascular disease. Furthermore, in testing the efficacy of compounds during clinical trials, a decrease in the level of the expression of these genes corresponds to a return from a disease condition to a normal state, and thereby indicates a positive effect of the compound. The cardiovascular diseases that may be so diagnosed, monitored in clinical trials, and treated include but are not limited to arteriosclerosis, ischemia, restenosis, and arterial inflammation.

The examples presented below, demonstrate the use of the cardiovascular disease experiments of the invention to identify cardiovascular disease target genes, and

demonstrates the use of marker genes in diagnostics and as surrogate markers for testing the efficacy of candidate drugs in basic research and in clinical trials.

5 “Gene or Genes” as used herein refers to the polynucleotides of SEQ ID NO. 1 to 74, as well as derivatives, fragments, analogs and homologues thereof, the polypeptides encoded thereby, the polypeptides of SEQ ID NO. 75 to 147 and the corresponding genomic transcription units which can be derived or identified with standard techniques well known in the art using the information disclosed in Tables 1 to 3. The GenBank and the UniGene accession numbers of the polynucleotide sequences
10 of the SEQ IDs NO. 1 to 74 are shown in the Tables 1 and 2.

The invention further relates to the use of:

- 15 a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;
- b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 20 c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 25 d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c);
- 30 e) an antisense molecule targeting one of the polynucleotide sequences specified in (a) to (d);

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- f) a purified polypeptide encoded by a polynucleotide sequence specified in (a) to (d)
- g) a purified polypeptide comprising at least one of the sequences of SEQ ID NO. 75 to 147;
- h) an antibody capable of binding to one of the polynucleotide specified in (a) to (d) or a polypeptide specified in (f) and (g)
- i) a reagent identified by any of the methods as specified below that modulates the amount or activity of a polynucleotide sequence specified in (a) to (d) or a polypeptide specified in (f) and (g)

for the preparation of compositions for the prevention, prediction, diagnosis, prognosis or a medicament for the treatment of a cardiovascular disease.

Polynucleotides

A „CVD gene“ polynucleotide can be single- or double-stranded and comprises a coding sequence or the complement of a coding sequence for a „CVD gene“ polypeptide. Degenerate nucleotide sequences encoding human „CVD gene“ polypeptides, as well as homologous nucleotide sequences which are at least about 50, 55, 60, 65, 70, preferably about 75, 90, 96, or 98% identical to the nucleotide sequences of SEQ ID NO.1 to 74 also are „CVD gene“ polynucleotides. Percent sequence identity between the sequences of two polynucleotides is determined using computer programs such as ALIGN which employ the FASTA algorithm, using an affine gap search with a gap open penalty of -12 and a gap extension penalty of -2. Complementary DNA (cDNA) molecules, species homologues, and variants of „CVD gene“ polynucleotides which encode biologically active „CVD gene“ polypeptides also are „CVD gene“ polynucleotides.

Preparation of Polynucleotides

A naturally occurring „CVD gene“ polynucleotide can be isolated free of other cellular components such as membrane components, proteins, and lipids. Polynucleotides can be made by a cell and isolated using standard nucleic acid purification techniques, or synthesized using an amplification technique, such as the polymerase chain reaction (PCR), or by using an automatic synthesizer. Methods for isolating polynucleotides are routine and are known in the art. Any such technique for obtaining a polynucleotide can be used to obtain isolated „CVD gene“ polynucleotides. For example, restriction enzymes and probes can be used to isolate polynucleotide fragments which comprises „CVD gene“ nucleotide sequences. Isolated polynucleotides are in preparations which are free or at least 70, 80, or 90% free of other molecules.

„CVD gene“ cDNA molecules can be made with standard molecular biology techniques, using „CVD gene“ mRNA as a template. Any RNA isolation technique which does not select against the isolation of mRNA may be utilized for the purification of such RNA samples. See, for example, Sambrook et al., (3).; and Ausubel, F. M. et al.,(4) , both of which are incorporated herein by reference in their entirety. Additionally, large numbers of tissue samples may readily be processed using techniques well known to those of skill in the art, such as, for example, the single-step RNA isolation process of Chomczynski, P. (1989, U.S. Pat. No. 4,843,155), which is incorporated herein by reference in its entirety.

„CVD gene“ cDNA molecules can thereafter be replicated using molecular biology techniques known in the art and disclosed in manuals such as Sambrook et al., (3) . An amplification technique, such as PCR, can be used to obtain additional copies of polynucleotides of the invention, using either human genomic DNA or cDNA as a template.

Alternatively, synthetic chemistry techniques can be used to synthesize „CVD gene“ polynucleotides. The degeneracy of the genetic code allows alternate nucleotide sequences to be synthesized which will encode a „CVD gene“ polypeptide or a biologically active variant thereof.

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Identification of differential expression

Transcripts within the collected RNA samples which represent RNA produced by differentially expressed genes may be identified by utilizing a variety of methods which are well known to those of skill in the art. For example, differential screening [Tedder, T. F. et al., (5)], subtractive hybridization [Hedrick, S. M. et al., (6); Lee, S. W. et al., (7)], and, preferably, differential display (Liang, P., and Pardee, A. B., 1993, U.S. Pat. No. 5,262,311, which is incorporated herein by reference in its entirety), may be utilized to identify nucleic acid sequences derived from genes that are differentially expressed.

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Differential screening involves the duplicate screening of a cDNA library in which one copy of the library is screened with a total cell cDNA probe corresponding to the mRNA population of one cell type while a duplicate copy of the cDNA library is screened with a total cDNA probe corresponding to the mRNA population of a second cell type. For example, one cDNA probe may correspond to a total cell cDNA probe of a cell type derived from a control subject, while the second cDNA probe may correspond to a total cell cDNA probe of the same cell type derived from an experimental subject. Those clones which hybridize to one probe but not to the other potentially represent clones derived from genes differentially expressed in the cell type of interest in control versus experimental subjects.

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Subtractive hybridization techniques generally involve the isolation of mRNA taken from two different sources, e.g., control and experimental tissue, the hybridization of the mRNA or single-stranded cDNA reverse-transcribed from the isolated mRNA, and the removal of all hybridized, and therefore double-stranded, sequences. The

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remaining non-hybridized, single-stranded cDNAs, potentially represent clones derived from genes that are differentially expressed in the two mRNA sources. Such single-stranded cDNAs are then used as the starting material for the construction of a library comprising clones derived from differentially expressed genes.

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The differential display technique describes a procedure, utilizing the well known polymerase chain reaction (PCR; the experimental embodiment set forth in Mullis, K. B., 1987, U.S. Pat. No. 4,683,202) which allows for the identification of sequences derived from genes which are differentially expressed. First, isolated RNA is reverse-transcribed into single-stranded cDNA, utilizing standard techniques which are well known to those of skill in the art. Primers for the reverse transcriptase reaction may include, but are not limited to, oligo dT-containing primers, preferably of the reverse primer type of oligonucleotide described below. Next, this technique uses pairs of PCR primers, as described below, which allow for the amplification of clones representing a random subset of the RNA transcripts present within any given cell. Utilizing different pairs of primers allows each of the mRNA transcripts present in a cell to be amplified. Among such amplified transcripts may be identified those which have been produced from differentially expressed genes.

20 The reverse oligonucleotide primer of the primer pairs may contain an oligo dT stretch of nucleotides, preferably eleven nucleotides long, at its 5' end, which hybridises to the poly(A) tail of mRNA or to the complement of a cDNA reverse transcribed from an mRNA poly(A) tail. Second, in order to increase the specificity of the reverse primer, the primer may contain one or more, preferably two, additional nucleotides at its 3' end. Because, statistically, only a subset of the mRNA derived sequences present in the sample of interest will hybridise to such primers, the additional nucleotides allow the primers to amplify only a subset of the mRNA derived sequences present in the sample of interest. This is preferred in that it allows more accurate and complete visualization and characterization of each of the bands representing amplified sequences.

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The forward primer may contain a nucleotide sequence expected, statistically, to have the ability to hybridise to cDNA sequences derived from the tissues of interest. The nucleotide sequence may be an arbitrary one, and the length of the forward oligonucleotide primer may range from about 9 to about 13 nucleotides, with about 10 nucleotides being preferred. Arbitrary primer sequences cause the lengths of the amplified partial cDNAs produced to be variable, thus allowing different clones to be separated by using standard denaturing sequencing gel electrophoresis. PCR reaction conditions should be chosen which optimise amplified product yield and specificity, and, additionally, produce amplified products of lengths which may be resolved utilizing standard gel electrophoresis techniques. Such reaction conditions are well known to those of skill in the art, and important reaction parameters include, for example, length and nucleotide sequence of oligonucleotide primers as discussed above, and annealing and elongation step temperatures and reaction times. The pattern of clones resulting from the reverse transcription and amplification of the mRNA of two different cell types is displayed via sequencing gel electrophoresis and compared. Differences in the two banding patterns indicate potentially differentially expressed genes.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. Randomly-primed libraries are preferable, in that they will contain more sequences which contain the 5' regions of genes. Use of a randomly primed library may be especially preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries can be useful for extension of sequence into 5' nontranscribed regulatory regions.

Commercially available capillary electrophoresis systems can be used to analyse the size or confirm the nucleotide sequence of PCR or sequencing products. For example, capillary sequencing can employ flowable polymers for electrophoretic separation, four different fluorescent dyes (one for each nucleotide) which are laser activated, and detection of the emitted wavelengths by a charge coupled device camera. Output/light intensity can be converted to electrical signal using appropriate

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software (e.g. GENOTYPER and Sequence NAVIGATOR, Perkin Elmer; ABI), and the entire process from loading of samples to computer analysis and electronic data display can be computer controlled. Capillary electrophoresis is especially preferable for the sequencing of small pieces of DNA which might be present in limited amounts in a particular sample.

Once potentially differentially expressed gene sequences have been identified via bulk techniques such as, for example, those described above, the differential expression of such putatively differentially expressed genes should be corroborated. Corroboration may be accomplished via, for example, such well known techniques as Northern analysis and/or RT-PCR. Upon corroboration, the differentially expressed genes may be further characterized, and may be identified as target and/or marker genes, as discussed, below.

Also, amplified sequences of differentially expressed genes obtained through, for example, differential display may be used to isolate full length clones of the corresponding gene. The full length coding portion of the gene may readily be isolated, without undue experimentation, by molecular biological techniques well known in the art. For example, the isolated differentially expressed amplified fragment may be labeled and used to screen a cDNA library. Alternatively, the labeled fragment may be used to screen a genomic library.

An analysis of the tissue distribution of the mRNA produced by the identified genes may be conducted, utilizing standard techniques well known to those of skill in the art. Such techniques may include, for example, Northern analyses and RT-PCR. Such analyses provide information as to whether the identified genes are expressed in tissues expected to contribute to cardiovascular disease. Such analyses may also provide quantitative information regarding steady state mRNA regulation, yielding data concerning which of the identified genes exhibits a high level of regulation in, preferably, tissues which may be expected to contribute to cardiovascular disease.

Such analyses may also be performed on an isolated cell population of a particular cell type derived from a given tissue. Additionally, standard in situ hybridization techniques may be utilized to provide information regarding which cells within a given tissue express the identified gene. Such analyses may provide information regarding the biological function of an identified gene relative to cardiovascular disease in instances wherein only a subset of the cells within the tissue is thought to be relevant to cardiovascular disease.

Extending Polynucleotides

In one embodiment of such a procedure for the identification and cloning of full length gene sequences, RNA may be isolated, following standard procedures, from an appropriate tissue or cellular source. A reverse transcription reaction may then be performed on the RNA using an oligonucleotide primer complimentary to the mRNA that corresponds to the amplified fragment, for the priming of first strand synthesis. Because the primer is anti-parallel to the mRNA, extension will proceed toward the 5' end of the mRNA. The resulting RNA hybrid may then be "tailed" with guanines using a standard terminal transferase reaction, the hybrid may be digested with RNAase H, and second strand synthesis may then be primed with a poly-C primer. Using the two primers, the 5' portion of the gene is amplified using PCR. Sequences obtained may then be isolated and recombined with previously isolated sequences to generate a full-length cDNA of the differentially expressed genes of the invention. For a review of cloning strategies and recombinant DNA techniques, see e.g., Sambrook et al., (3); and Ausubel et al., (4).

Various PCR-based methods can be used to extend the nucleic acid sequences disclosed herein to detect upstream sequences such as promoters and regulatory elements. For example, restriction site PCR uses universal primers to retrieve unknown sequence adjacent to a known locus [Sarkar,(8)]. Genomic DNA is first amplified in the presence of a primer to a linker sequence and a primer specific to the known region. The amplified sequences are then subjected to a second round of PCR

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with the same linker primer and another specific primer internal to the first one. Products of each round of PCR are transcribed with an appropriate RNA polymerase and sequenced using reverse transcriptase.

5 Inverse PCR also can be used to amplify or extend sequences using divergent primers based on a known region [Triglia et al., (9)]. Primers can be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences Inc., Plymouth, Minn.), to be 2230 nucleotides in length, to have a GC content of 50% or more, and to anneal to the target sequence at
10 temperatures about 68-72 °C. The method uses several restriction enzymes to generate a suitable fragment in the known region of a gene. The fragment is then circularized by intramolecular ligation and used as a PCR template.

Another method which can be used is capture PCR, which involves PCR ampli-
15 fication of DNA fragments adjacent to a known sequence in human and yeast artificial chromosome DNA [Lagerstrom et al.,(10)]. In this method, multiple restriction enzyme digestions and ligations also can be used to place an engineered double-stranded sequence into an unknown fragment of the DNA molecule before performing PCR.

20 Another method which can be used to retrieve unknown sequences is that of Parker et al., (11). Additionally, PCR, nested primers, and PROMOTERFINDER libraries (CLONTECH, Palo Alto, Calif.) can be used to walk genomic DNA (CLONTECH, Palo Alto, Calif.). This process avoids the need to screen libraries and is useful in
25 finding intron/exon junctions.

The sequences of the identified genes may be used, utilizing standard techniques, to place the genes onto genetic maps, e.g., mouse [Copeland & Jenkins, (12)] and human genetic maps [Cohen, et al., (13)]. Such mapping information may yield
30 information regarding the genes' importance to human disease by, for example,

identifying genes which map near genetic regions to which known genetic cardiovascular disease tendencies map.

Identification of Polynucleotide Variants and Homologues

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Variants and homologues of the „CVD gene“ polynucleotides described above also are „CVD gene“ polynucleotides. Typically, homologous „CVD gene“ polynucleotide sequences can be identified by hybridization of candidate polynucleotides to known „CVD gene“ polynucleotides under stringent conditions, as is known in the art. For example, using the following wash conditions: 2X SSC (0.3 M NaCl, 0.03 M sodium citrate, pH 7.0), 0.1% SDS, room temperature twice, 30 minutes each; then 10 2X SSC, 0.1% SDS, 50 EC once, 30 minutes; then 2X SSC, room temperature twice, 10 minutes each homologous sequences can be identified which contain at most about 25-30% basepair mismatches. More preferably, homologous nucleic acid strands contain 15-25% basepair mismatches, even more preferably 5-15% basepair mismatches. 15

Species homologues of the „CVD gene“ polynucleotides disclosed herein also can be identified by making suitable probes or primers and screening cDNA expression libraries from other species, such as mice, monkeys, or yeast. Human variants of 20 „CVD gene“ polynucleotides can be identified, for example, by screening human cDNA expression libraries. It is well known that the T_m of a double-stranded DNA decreases by 1-1.5 °C with every 1% decrease in homology [Bonner et al., (14)]. Variants of human „CVD gene“ polynucleotides or „CVD gene“ polynucleotides of 25 other species can therefore be identified by hybridizing a putative homologous „CVD gene“ polynucleotide with a polynucleotide having a nucleotide sequence of one of the sequences of the SEQ ID Nos:1 to 74 or the complement thereof to form a test hybrid. The melting temperature of the test hybrid is compared with the melting temperature of a hybrid comprising polynucleotides having perfectly complementary 30 nucleotide sequences, and the number or percent of basepair mismatches within the test hybrid is calculated.

Nucleotide sequences which hybridize to „CVD gene“ polynucleotides or their complements following stringent hybridization and/or wash conditions also are „CVD gene“ polynucleotides. Stringent wash conditions are well known and understood in the art and are disclosed, for example, in Sambrook et al., (3). Typically, for stringent hybridization conditions a combination of temperature and salt concentration should be chosen that is approximately 12-20°C below the calculated T_m of the hybrid under study. The T_m of a hybrid between a „CVD gene“ polynucleotide having a nucleotide sequence of one of the sequences of the SEQ ID NOS: 1 to 74 or the complement thereof and a polynucleotide sequence which is at least about 50, preferably about 75, 90, 96, or 98% identical to one of those nucleotide sequences can be calculated, for example, using the equation of Bolton and McCarthy, (15):

$$T_m = 81.5^{\circ}\text{C} - 16.6(\log_{10}[\text{Na}^+]) + 0.41(\%G + C) - 0.63(\%\text{formamide}) - 600/l,$$

where l = the length of the hybrid in basepairs.

Stringent wash conditions include, for example, 4X SSC at 65°C, or 50% formamide, 4X SSC at 28 °C, or 0.5X SSC, 0.1% SDS at 65°C. Highly stringent wash conditions include, for example, 0.2X SSC at 65°C.

The biological function of the identified genes may be more directly assessed by utilizing relevant in vivo and in vitro systems. In vivo systems may include, but are not limited to, animal systems which naturally exhibit cardiovascular disease predisposition, or ones which have been engineered to exhibit such symptoms, including but not limited to the apoE-deficient arteriosclerosis mouse model [Plump et al., (16)].

Polypeptides

“CVD gene” polypeptides according to the invention comprise an amino acid selected from the amino acid sequence which are encoded by any of the polynucleotide sequences of the SEQ ID NOS: 1 to 74 or derivatives, fragments, analogues and homologues thereof. A “CVD gene” polypeptide of the invention therefore can be a portion, a full-length, or a fusion protein comprising all or a portion of a “CVD gene” polypeptide.

10 Protein Purification

„CVD gene“ polypeptides can be purified from any cell which expresses the enzyme, including host cells which have been transfected with „CVD gene“ expression constructs. Blood vessels are an especially useful source of „CVD gene“ polypeptides. A purified „CVD gene“ polypeptide is separated from other compounds which normally associate with the „CVD gene“ polypeptide in the cell, such as certain proteins, carbohydrates, or lipids, using methods well-known in the art. Such methods include, but are not limited to, size exclusion chromatography, ammonium sulfate fractionation, ion exchange chromatography, affinity chromatography, and preparative gel electrophoresis. A preparation of purified „CVD gene“ polypeptides is at least 80% pure; preferably, the preparations are 90%, 95%, or 99% pure. Purity of the preparations can be assessed by any means known in the art, such as SDS-polyacrylamide gel electrophoresis.

25 Expression of Polynucleotides

To express a „CVD gene“ polynucleotide, the polynucleotide can be inserted into an expression vector which contains the necessary elements for the transcription and translation of the inserted coding sequence. Methods which are well known to those skilled in the art can be used to construct expression vectors containing sequences encoding „CVD gene“ polypeptides and appropriate transcriptional and translational

control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques, and in vivo genetic recombination. Such techniques are described, for example, in Sambrook et al., (3) and in Ausubel et al., (4).

5 A variety of expression vector/host systems can be utilized to contain and express sequences encoding a „CVD gene“ polypeptide. These include, but are not limited to, microorganisms, such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression
10 vectors, insect cell systems infected with virus expression vectors (e.g., baculovirus), plant cell systems transformed with virus expression vectors (e.g., cauliflower mosaic virus, CaMV; tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids), or animal cell systems.

The control elements or regulatory sequences are those regions of the vector
15 enhancers, promoters, 5' and 3' untranslated regions which interact with host cellular proteins to carry out transcription and translation. Such elements can vary in their strength and specificity. Depending on the vector system and host utilized, any number of suitable transcription and translation elements, including constitutive and inducible promoters, can be used. For example, when cloning in bacterial systems,
20 inducible promoters such as the hybrid lacZ promoter of the BLUESCRIPT phagemid (Stratagene, LaJolla, Calif.) or pSPORT1 plasmid (Life Technologies) and the like can be used. The baculovirus polyhedrin promoter can be used in insect cells. Promoters or enhancers derived from the genomes of plant cells (e.g., heat shock, RUBISCO, and storage protein genes) or from plant viruses (e.g., viral promoters or
25 leader sequences) can be cloned into the vector. In mammalian cell systems, promoters from mammalian genes or from mammalian viruses are preferable. If it is necessary to generate a cell line that contains multiple copies of a nucleotide sequence encoding a „CVD gene“ polypeptide, vectors based on SV40 or EBV can be used with an appropriate selectable marker.

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Obtaining Polypeptides

„CVD gene“ polypeptides can be obtained, for example, by purification from human cells, by expression of „CVD gene“ polynucleotides, or by direct chemical synthesis.

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Biologically Active Variants

„CVD gene“ polypeptide variants which are biologically active, i.e., retain an „CVD gene“ activity, also are „CVD gene“ polypeptides. Preferably, naturally or non-naturally occurring „CVD gene“ polypeptide variants have amino acid sequences which are at least about 60, 65, or 70, preferably about 75, 80, 85, 90, 92, 94, 96, or 98% identical to the amino acid sequence of any of the sequences of the SEQ ID NOS: 75 to 147 or a fragment thereof. Percent identity between a putative „CVD gene“ polypeptide variant and an amino acid sequence encoded by any of the polynucleotide sequences of the SEQ ID NOS: 75 to 147 is determined using the Needleman/Wunsch algorithm (108) with the substitutions-matrix BLOSUM62 (109) and a gap creation penalty of 8 and a gap extension penalty of 2.

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Variations in percent identity can be due, for example, to amino acid substitutions, insertions, or deletions. Amino acid substitutions are defined as one for one amino acid replacements. They are conservative in nature when the substituted amino acid has similar structural and/or chemical properties. Examples of conservative replacements are substitution of a leucine with an isoleucine or valine, an aspartate with a glutamate, or a threonine with a serine.

25

Amino acid insertions or deletions are changes to or within an amino acid sequence. They typically fall in the range of about 1 to 5 amino acids. Guidance in determining which amino acid residues can be substituted, inserted, or deleted without abolishing biological or immunological activity of a „CVD gene“ polypeptide can be found using computer programs well known in the art, such as DNASTAR software.

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Whether an amino acid change results in a biologically active „CVD gene“ polypeptide can readily be determined by assaying for „CVD gene“ activity, as

described for example, in the specific Examples, below. Larger insertions or deletions can also be caused by alternative splicing. Protein domains can be inserted or deleted without altering the main activity of the protein.

5 Fusion Proteins

Fusion proteins are useful for generating antibodies against „CVD gene“ polypeptide amino acid sequences and for use in various assay systems. For example, fusion proteins can be used to identify proteins which interact with portions of a „CVD gene“ polypeptide. Protein affinity chromatography or library-based assays for
10 protein-protein interactions, such as the yeast two-hybrid or phage display systems, can be used for this purpose. Such methods are well known in the art and also can be used as drug screens.

15 A „CVD gene“ polypeptide fusion protein comprises two polypeptide segments fused together by means of a peptide bond. The first polypeptide segment comprises at least 25, 50, 75, 100, 150, 200, 300, 400, 500, 600, 700 or 750 contiguous amino acids of an amino acid sequence encoded by any polynucleotide sequences of the SEQ ID NOS: 1 to 74 or of a biologically active variant, such as those described
20 above. The first polypeptide segment also can comprise full-length „CVD gene“.

The second polypeptide segment can be a full-length protein or a protein fragment. Proteins commonly used in fusion protein construction include β -galactosidase, -glucuronidase, green fluorescent protein (GFP), autofluorescent proteins, including
25 blue fluorescent protein (BFP), glutathione-S-transferase (GST), luciferase, horseradish peroxidase (HRP), and chloramphenicol acetyltransferase (CAT). Additionally, epitope tags are used in fusion protein constructions, including histidine (His) tags, FLAG tags, influenza hemagglutinin (HA) tags, Myc tags, VSV-G tags, and thioredoxin (Trx) tags. Other fusion constructions can include maltose
30 binding protein (MBP), S-tag, Lex a DNA binding domain (DBD) fusions, GAL4 DNA binding domain fusions, and herpes simplex virus (HSV) BP16 protein fusions.

A fusion protein also can be engineered to contain a cleavage site located between the „CVD gene“ polypeptide-encoding sequence and the heterologous protein sequence, so that the „CVD gene“ polypeptide can be cleaved and purified away from the heterologous moiety.

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A fusion protein can be synthesized chemically, as is known in the art. Preferably, a fusion protein is produced by covalently linking two polypeptide segments or by standard procedures in the art of molecular biology. Recombinant DNA methods can be used to prepare fusion proteins, for example, by making a DNA construct which comprises coding sequences selected from any of the polynucleotide sequences of the SEQ ID NOS:1 to in proper reading frame with nucleotides encoding the second polypeptide segment and expressing the DNA construct in a host cell, as is known in the art. Many kits for constructing fusion proteins are available from companies such as Promega Corporation (Madison, WI), Stratagene (La Jolla, CA), CLONTECH (Mountain View, CA), Santa Cruz Biotechnology (Santa Cruz, CA), MBL International Corporation (MIC; Watertown, MA), and Quantum Biotechnologies (Montreal, Canada; 1-888-DNA-KITS).

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Identification of Species Homologs

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Species homologues of human a „CVD gene“ polypeptide can be obtained using „CVD gene“ polypeptide polynucleotides (described below) to make suitable probes or primers for screening cDNA expression libraries from other species, such as mice, monkeys, or yeast, identifying cDNAs which encode homologs of a „CVD gene“ polypeptide, and expressing the cDNAs as is known in the art.

25

Bacterial and Yeast Expression Systems

In bacterial systems, a number of expression vectors can be selected depending upon the use intended for the „CVD gene“ polypeptide. For example, when a large quantity of the „CVD gene“ polypeptide is needed for the induction of antibodies, vectors which direct high level expression of fusion proteins that are readily purified

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can be used. Such vectors include, but are not limited to, multifunctional *E. coli* cloning and expression vectors such as BLUESCRIPT (Stratagene). In a BLUESCRIPT vector, a sequence encoding the „CVD gene“ polypeptide can be ligated into the vector in frame with sequences for the amino terminal Met and the subsequent 7 residues of β -galactosidase so that a hybrid protein is produced. pIN vectors [Van Heeke & Schuster, (17)] or pGEX vectors (Promega, Madison, Wis.) also can be used to express foreign polypeptides as fusion proteins with glutathione S-transferase (GST). In general, such fusion proteins are soluble and can easily be purified from lysed cells by adsorption to glutathione agarose beads followed by elution in the presence of free glutathione. Proteins made in such systems can be designed to include heparin, thrombin, or factor Xa protease cleavage sites so that the cloned polypeptide of interest can be released from the GST moiety at will.

In the yeast *Saccharomyces cerevisiae*, a number of vectors containing constitutive or inducible promoters such as alpha factor, alcohol oxidase, and PGH can be used. For reviews, see Ausubel et al., (4) and Grant et al., (18).

Plant and Insect Expression Systems

If plant expression vectors are used, the expression of sequences encoding „CVD gene“ polypeptides can be driven by any of a number of promoters. For example, viral promoters such as the 35S and 19S promoters of CaMV can be used alone or in combination with the omega leader sequence from TMV [Takamatsu, (19)]. Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters can be used [Coruzzi et al., (19); Broglie et al., (21); Winter et al., (22)]. These constructs can be introduced into plant cells by direct DNA transformation or by pathogen-mediated transfection. Such techniques are described in a number of generally available reviews (e.g., Hobbs or Murray, in MCGRAW HILL YEARBOOK OF SCIENCE AND TECHNOLOGY, (23)).

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An insect system also can be used to express a „CVD gene“ polypeptide. For example, in one such system *Autographa californica* nuclear polyhedrosis virus (AcNPV) is used as a vector to express foreign genes in *Spodoptera frugiperda* cells or in *Trichoplusia* larvae. Sequences encoding „CVD gene“ polypeptides can be cloned into a nonessential region of the virus, such as the polyhedrin gene, and placed under control of the polyhedrin promoter. Successful insertion of „CVD gene“ polypeptides will render the polyhedrin gene inactive and produce recombinant virus lacking coat protein. The recombinant viruses can then be used to infect *S. frugiperda* cells or *Trichoplusia* larvae in which „CVD gene“ polypeptides can be expressed [Engelhard et al., (24)].

Mammalian Expression Systems

A number of viral-based expression systems can be used to express „CVD gene“ polypeptides in mammalian host cells. For example, if an adenovirus is used as an expression vector, sequences encoding „CVD gene“ polypeptides can be ligated into an adenovirus transcription/translation complex comprising the late promoter and tripartite leader sequence. Insertion in a nonessential E1 or E3 region of the viral genome can be used to obtain a viable virus which is capable of expressing a „CVD gene“ polypeptide in infected host cells [Logan & Shenk, (25)]. If desired, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, can be used to increase expression in mammalian host cells.

Human artificial chromosomes (HACs) also can be used to deliver larger fragments of DNA than can be contained and expressed in a plasmid. HACs of 6M to 10M are constructed and delivered to cells via conventional delivery methods (e.g., liposomes, polycationic amino polymers, or vesicles).

Specific initiation signals also can be used to achieve more efficient translation of sequences encoding „CVD gene“ polypeptides. Such signals include the ATG initiation codon and adjacent sequences. In cases where sequences encoding a „CVD

gene" polypeptide, its initiation codon, and upstream sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals (including the ATG initiation codon) should be provided. The initiation codon should be in the correct reading frame to ensure translation of the entire insert. Exogenous translational elements and initiation codons can be of various origins, both natural and synthetic. The efficiency of expression can be enhanced by the inclusion of enhancers which are appropriate for the particular cell system which is used [Scharf et al., (26)].

Host Cells

A host cell strain can be chosen for its ability to modulate the expression of the inserted sequences or to process the expressed „CVD gene" polypeptide in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Posttranslational processing which cleaves a "prepro" form of the polypeptide also can be used to facilitate correct insertion, folding and/or function. Different host cells which have specific cellular machinery and characteristic mechanisms for Post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38), are available from the American Type Culture Collection (ATCC; 10801 University Boulevard, Manassas, VA 20110-2209) and can be chosen to ensure the correct modification and processing of the foreign protein.

Stable expression is preferred for long-term, high-yield production of recombinant proteins. For example, cell lines which stably express „CVD gene" polypeptides can be transformed using expression vectors which can contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells can be allowed to grow for 12 days in an enriched medium before they are switched to a

selective medium. The purpose of the selectable marker is to confer resistance to selection, and its presence allows growth and recovery of cells which successfully express the introduced „CVD gene“ sequences. Resistant clones of stably transformed cells can be proliferated using tissue culture techniques appropriate to the cell type. See, for example, R.I. Freshney, (27).

Any number of selection systems can be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase (Wigler et al., (28)) and adenine phosphoribosyltransferase [Lowy et al., (29)] genes which can be employed in tk⁻ or aprt⁻ cells, respectively. Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, dhfr confers resistance to methotrexate [Wigler et al., (30)], npt confers resistance to the aminoglycosides, neomycin and G418 [Colbere-Garapin et al., (31)], and als and pat confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. Additional selectable genes have been described. For example, trpB allows cells to utilize indole in place of tryptophan, or hisD, which allows cells to utilize histinol in place of histidine [Hartman & Mulligan, (32)]. Visible markers such as anthocyanins, β -glucuronidase and its substrate GUS, and luciferase and its substrate luciferin, can be used to identify transformants and to quantify the amount of transient or stable protein expression attributable to a specific vector system [Rhodes et al., (33)].

Detecting Expression and gene product

Although the presence of marker gene expression suggests that the „CVD gene“ polynucleotide is also present, its presence and expression may need to be confirmed. For example, if a sequence encoding a „CVD gene“ polypeptide is inserted within a marker gene sequence, transformed cells containing sequences which encode a „CVD gene“ polypeptide can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding a „CVD gene“ polypeptide under the control of a single promoter. Expression of the

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marker gene in response to induction or selection usually indicates expression of the „CVD gene“ polynucleotide.

Alternatively, host cells which contain a „CVD gene“ polynucleotide and which
5 express a „CVD gene“ polypeptide can be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridization and protein bioassay or immunoassay techniques which include membrane, solution, or chip-based technologies for the detection and/or quantification of nucleic acid or protein. For example, the presence
10 of a polynucleotide sequence encoding a „CVD gene“ polypeptide can be detected by DNA-DNA or DNA-RNA hybridization or amplification using probes or fragments or fragments of polynucleotides encoding a „CVD gene“ polypeptide. Nucleic acid amplification-based assays involve the use of oligonucleotides selected from sequences encoding a „CVD gene“ polypeptide to detect transformants which
15 contain a „CVD gene“ polynucleotide.

A variety of protocols for detecting and measuring the expression of a „CVD gene“ polypeptide, using either polyclonal or monoclonal antibodies specific for the polypeptide, are known in the art. Examples include enzyme-linked immunosorbent
20 assay (ELISA), radioimmunoassay (RIA), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay using monoclonal antibodies reactive to two non-interfering epitopes on a „CVD gene“ polypeptide can be used, or a competitive binding assay can be employed. These and other assays are described in Hampton et al., (34) and Maddox et al., (35).

25 A wide variety of labels and conjugation techniques are known by those skilled in the art and can be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding „CVD gene“ polypeptides include oligo labeling, nick
30 translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, sequences encoding a „CVD gene“ polypeptide can be cloned into a

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vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and can be used to synthesise RNA probes in vitro by addition of labelled nucleotides and an appropriate RNA polymerase such as T7, T3, or SP6. These procedures can be conducted using a variety of commercially available kits (Amersham Pharmacia Biotech, Promega, and US Biochemical). Suitable reporter molecules or labels which can be used for ease of detection include radio-nuclides, enzymes, and fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

10 Expression and Purification of Polypeptides

Host cells transformed with nucleotide sequences encoding a „CVD gene“ polypeptide can be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The polypeptide produced by a transformed cell can be secreted or stored intracellular depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode „CVD gene“ polypeptides can be designed to contain signal sequences which direct secretion of soluble „CVD gene“ polypeptides through a prokaryotic or eukaryotic cell membrane or which direct the membrane insertion of membrane-bound „CVD gene“ polypeptide.

As discussed above, other constructions can be used to join a sequence encoding a „CVD gene“ polypeptide to a nucleotide sequence encoding a polypeptide domain which will facilitate purification of soluble proteins. Such purification facilitating domains include, but are not limited to, metal chelating peptides such as histidine-tryptophan modules that allow purification on immobilized metals, protein A domains that allow purification on immobilized immunoglobulin, and the domain utilized in the FLAGS extension/affinity purification system (Immunex Corp., Seattle, Wash.). Inclusion of cleavable linker sequences such as those specific for Factor Xa or enterokinase (Invitrogen, San Diego, CA) between the purification domain and the „CVD gene“ polypeptide also can be used to facilitate purification.

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One such expression vector provides for expression of a fusion protein containing a „CVD gene“ polypeptide and 6 histidine residues preceding a thioredoxin or an enterokinase cleavage site. The histidine residues facilitate purification by IMAC (immobilized metal ion affinity chromatography, as described in Porath et al., (36),
5 while the enterokinase cleavage site provides a means for purifying the „CVD gene“ polypeptide from the fusion protein. Vectors which contain fusion proteins are disclosed in Kroll et al., (37).

Chemical Synthesis

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Sequences encoding a „CVD gene“ polypeptide can be synthesised, in whole or in part, using chemical methods well known in the art (see Caruthers et al., (38) and Horn et al., (39). Alternatively, a „CVD gene“ polypeptide itself can be produced using chemical methods to synthesise its amino acid sequence, such as by direct
15 peptide synthesis using solid-phase techniques [Merrifield, (40) and Roberge et al., (41)]. Protein synthesis can be performed using manual techniques or by automation. Automated synthesis can be achieved, for example, using Applied Biosystems 431A Peptide Synthesizer (Perkin Elmer). Optionally, fragments of „CVD gene“ polypeptides can be separately synthesized and combined using chemical methods to
20 produce a full-length molecule.

The newly synthesized peptide can be substantially purified by preparative high performance liquid chromatography [Creighton, (42)]. The composition of a synthetic „CVD gene“ polypeptide can be confirmed by amino acid analysis or
25 sequencing (e.g., the Edman degradation procedure; see Creighton, (42). Additionally, any portion of the amino acid sequence of the „CVD gene“ polypeptide can be altered during direct synthesis and/or combined using chemical methods with sequences from other proteins to produce a variant polypeptide or a fusion protein.

Production of Altered Polypeptides

As will be understood by those of skill in the art, it may be advantageous to produce „CVD gene“ polypeptide-encoding nucleotide sequences possessing non-natural occurring codons. For example, codons preferred by a particular prokaryotic or eukaryotic host can be selected to increase the rate of protein expression or to produce an RNA transcript having desirable properties, such as a half-life which is longer than that of a transcript generated from the naturally occurring sequence.

The nucleotide sequences disclosed herein can be engineered using methods generally known in the art to alter „CVD gene“ polypeptide-encoding sequences for a variety of reasons, including but not limited to, alterations which modify the cloning, processing, and/or expression of the polypeptide or mRNA product. DNA shuffling by random fragmentation and PCR re-assembly of gene fragments and synthetic oligonucleotides can be used to engineer the nucleotide sequences. For example, site-directed mutagenesis can be used to insert new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, introduce mutations, and so forth.

Diagnostic and Prognostic Assays

The present invention provides method for determining whether a subject is at risk for developing cardiovascular disease and arteriosclerosis in particular by detecting the disclosed biomarkers, i.e., the disclosed polynucleotide markers comprising any of the polynucleotides sequences of the SEQ ID NOS:1 to 74 and/or the polypeptide markers encoded thereby or comprising any of the polypeptide sequences of the SEQ ID NOS: 75 to 147 for cardiovascular disease and arteriosclerosis in particular in particular encoded thereby.

In clinical applications, biological samples can be screened for the presence and/or absence of the biomarkers identified herein. Such samples are for example needle

biopsy cores, surgical resection samples, or body fluids like serum and urine. For example, these methods include obtaining a biopsy, which is optionally fractionated by cryostat sectioning to enrich diseased cells to about 80% of the total cell population. In certain embodiments, nucleic acids extracted from these samples may be amplified using techniques well known in the art. The expression levels of selected markers detected would be compared with statistically valid groups of diseased and healthy samples.

In one embodiment the diagnostic method comprises determining whether a subject has an abnormal mRNA and/or protein level of the disclosed markers, such as by Northern blot analysis, reverse transcription-polymerase chain reaction (RT-PCR), in situ hybridization, immunoprecipitation, Western blot hybridization, or immunohistochemistry. According to the method, cells are obtained from a subject and the levels of the disclosed biomarkers, protein or mRNA level, is determined and compared to the level of these markers in a healthy subject. An abnormal level of the biomarker polypeptide or mRNA levels is likely to be indicative of cardiovascular disease such as arteriosclerosis.

1. Polynucleotide detection

In one embodiment, the method for the diagnosis or prognosis of cardiovascular disease is done by the detection of:

- (a) polynucleotide selected from the polynucleotides of the SEQ ID NOS: 1 to 74;
- (b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- (c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes

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a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

- (d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c);

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in a biological sample comprising the following steps: hybridizing any polynucleotide specified in (a) to (d) to a nucleic acid material of a biological sample, thereby forming a hybridization complex; and detecting said hybridization complex.

- 10 In another embodiment the method for the diagnosis or prognosis of cardiovascular disease is done as just described but, wherein before hybridization, the nucleic acid material of the biological sample is amplified.

- 15 In another embodiment the method for the diagnosis or prognosis of cardiovascular disease is done by the detection of:

- (a) a polynucleotide selected from the polynucleotides of the SEQ ID NOS: 1 to 74;
- (b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 20 (c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 25 (d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c);
- (e) a polypeptide encoded by a polynucleotide sequence specified in (a) to (d)

comprising the steps of contacting a biological sample with a reagent which specifically interacts with the polynucleotide specified in (a) to (d) or the polypeptide specified in (e).

5 2. DNA array technology

In one embodiment, the present Invention also provides a method wherein polynucleotide probes are immobilized on a DNA chip in an organised array. Oligonucleotides can be bound to a solid Support by a variety of processes, including
10 lithography. For example a chip can hold up to 4100,00 oligonucleotides (GeneChip, Affymetrix). These polynucleotide probes comprise a nucleotide sequence at least about 12 nucleotides in length, preferably at least about 15 nucleotides, more preferably at least about 25 nucleotides, and most preferably at least about 40 nucleotides, and up to all or nearly all of a sequence which is complementary to a
15 portion of the coding sequence of a marker polynucleotide sequence selected from the polynucleotides of the SEQ ID NOS:1 to 74 and is differentially expressed in cardiovascular tissue. The present invention provides significant advantages over the available tests for cardiovascular disease, such as arteriosclerosis, because it increases the reliability of the test by providing an array of polynucleotide markers on
20 a single chip.

The method includes obtaining a biopsy of an affected artery, which is optionally fractionated by cryostat sectioning to enrich diseased cells to about 80% of the total cell population and the use of body fluids such as serum or urine. The DNA or RNA
25 is then extracted, amplified, and analysed with a DNA chip to determine the presence of absence of the marker polynucleotide sequences. In one embodiment, the polynucleotide probes are spotted onto a substrate in a two-dimensional matrix or array. samples of polynucleotides can be labeled and then hybridised to the probes. Double-stranded polynucleotides, comprising the labeled sample polynucleotides
30 bound to probe polynucleotides, can be detected once the unbound portion of the sample is washed away.

The probe polynucleotides can be spotted on substrates including glass, nitrocellulose, etc. The probes can be bound to the Substrate by either covalent bonds or by non-specific interactions, such as hydrophobic interactions. The sample polynucleotides can be labelled using radioactive labels, fluorophores, chromophores, etc. Techniques for constructing arrays and methods of using these arrays are described in EP No. 0 799 897; PCT No. WO 97/29212; PCT No. WO 97/27317; EP No. 0 785 280; PCT No. WO 97/02357; U.S. Pat. No. 5,593,839; U.S. Pat. No. 5,578,832; EP No. 0 728 520; U.S. Pat. No. 5,599,695; EP No. 0 721 016; U.S. Pat. No. 5,556,752; PCT No. WO 95/22058; and U.S. Pat. No. 5,631,734. Further, arrays can be used to examine differential expression of genes and can be used to determine gene function. For example, arrays of the instant polynucleotide sequences can be used to determine if any of the polynucleotide sequences are differentially expressed between normal cells and diseased cells, for example. High expression of a particular message in a diseased sample, which is not observed in a corresponding normal sample, can indicate a cardiovascular disease specific protein.

Accordingly, in one aspect, the invention provides probes and primers that are specific to the unique polynucleotide markers disclosed herein.

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In one embodiment, the method comprises using a polynucleotide probe to determine the presence of cardiovascular disease cells in a tissue from a patient. Specifically, the method comprises:

- 1) providing a polynucleotide probe comprising a nucleotide sequence at least 12 nucleotides in length, preferably at least 15 nucleotides, more preferably, 25 nucleotides, and most preferably at least 40 nucleotides, and up to all or nearly all of the coding sequence which is complementary to a portion of the coding sequence of a polynucleotide selected from the polynucleotides or the SEQ ID NOS:1 to 74 or a sequence complementary thereto and is
- 2) differentially expressed in cardiovascular disease, such as arteriosclerosis ;

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- 3) obtaining a tissue sample from a patient with cardiovascular disease and arteriosclerosis in particular;
- 4) providing a second tissue sample from a patient with no cardiovascular disease;
- 5) contacting the polynucleotide probe under stringent conditions with RNA of each of said first and second tissue samples (e.g., in a Northern blot or in situ hybridization assay); and
- 6) comparing (a) the amount of hybridization of the probe with RNA of the first tissue sample, with (b) the amount of hybridization of the probe with RNA of the second tissue sample;

wherein a statistically significant difference in the amount of hybridization with the RNA of the first tissue sample as compared to the amount of hybridization with the RNA of the second tissue sample is indicative of cardiovascular disease and arteriosclerosis in particular in the first tissue sample.

3. Detection of variant polynucleotide sequence

In yet another embodiment, the invention provides methods for determining whether a subject is at risk for developing a disease, such as a predisposition to develop cardiovascular disease, for example arteriosclerosis, associated with an aberrant activity of any one of the polypeptides encoded by any of the polynucleotides of the SEQ ID NOS:1 to 74, wherein the aberrant activity of the polypeptide is characterised by detecting the presence or absence of a genetic lesion characterised by at least one of these:

- (i) an alteration affecting the integrity of a gene encoding a marker polypeptides, or
- (ii) the misexpression of the encoding polynucleotide.

To illustrate, such genetic lesions can be detected by ascertaining the existence of at least one of these:

- I. a deletion of one or more nucleotides from the polynucleotide sequence
- 5 II. an addition of one or more nucleotides to the polynucleotide sequence
- III. a Substitution of one or more nucleotides of the polynucleotide sequence
- IV. a gross chromosomal rearrangement of the polynucleotide sequence
- V. a gross alteration in the level of a messenger RNA transcript of the polynucleotide sequence
- 10 VI. aberrant modification of the polynucleotide sequence, such as of the methylation Pattern of the genomic DNA
- VII. the presence of a non-wild type splicing Pattern of a messenger RNA transcript of the gene
- VIII. a non-wild type level of the marker polypeptide
- 15 IX. allelic loss of the gene
- X. inappropriate post-translational modification of the marker polypeptide

The present Invention provides assay techniques for detecting mutations in the encoding polynucleotide sequence. These methods include, but are not limited to, methods involving sequence analysis, Southern blot hybridization, restriction enzyme site mapping, and methods involving detection of absence of nucleotide pairing between the polynucleotide to be analyzed and a probe.

Specific diseases or disorders, e.g., genetic diseases or disorders, are associated with specific allelic variants of polymorphic regions of certain genes, which do not necessarily encode a mutated Protein. Thus, the presence of a specific allelic variant of a polymorphic region of a gene in a subject can render the subject susceptible to developing a specific disease or disorder. Polymorphic regions in genes, can be identified, by determining the nucleotide sequence of genes in populations of individuals. If a polymorphic region is identified, then the link with a specific disease can be determined by studying specific populations of individuals, e.g. individuals

which developed a specific disease, such as cardiovascular disease. A polymorphic region can be located in any region of a gene, e.g., exons, in coding or non coding regions of exons, introns, and promoter region.

5 In an exemplary embodiment, there is provided a polynucleotide composition comprising a polynucleotide probe including a region of nucleotide sequence which is capable of hybridising to a sense or antisense sequence of a gene or naturally occurring mutants thereof, or 5' or 3' flanking sequences or intronic sequences naturally associated with the subject genes or naturally occurring mutants thereof.

10 The polynucleotide of a cell is rendered accessible for hybridization, the probe is contacted with the polynucleotide of the sample, and the hybridization of the probe to the sample polynucleotide is detected. Such techniques can be used to detect lesions or allelic variants at either the genomic or mRNA level, including deletions, substitutions, etc., as well as to determine mRNA transcript levels.

15 A preferred detection method is allele specific hybridization using probes overlapping the mutation or polymorphic site and having about 5, 10, 20, 25, or 30 nucleotides around the mutation or polymorphic region. In a preferred embodiment of the invention, several probes capable of hybridising specifically to allelic variants

20 are attached to a solid phase support, e.g., a "chip". Mutation detection analysis using these chips comprising oligonucleotides, also termed "DNA probe arrays" is described e.g., in Cronin et al. (43). In one embodiment, a chip comprises all the allelic variants of at least one polymorphic region of a gene. The solid phase support is then contacted with a test polynucleotide and hybridization to the specific probes is

25 detected. Accordingly, the identity of numerous allelic variants of one or more genes can be identified in a simple hybridization experiment.

In certain embodiments, detection of the lesion comprises utilizing the probe/primer in a polymerase chain reaction (PCR) (see, e.g. U.S. Patent Nos. 4,683,195 and

30 4,683,202), such as anchor PCR or RACE PCR, or, alternatively, in a ligase chain reaction (LCR) (see, e.g., Landegran et al., (44) and Nakazawa et al., (45)], the latter

of which can be particularly useful for detecting point mutations in the gene (see Abravaya et al., (46)). In a merely illustrative embodiment, the method includes the steps of (i) collecting a sample of cells from a patient, (ii) isolating polynucleotide (e.g., genomic, mRNA or both) from the cells of the sample, (iii) contacting the polynucleotide sample with one or more primers which specifically hybridise to a polynucleotide sequence under conditions such that hybridization and amplification of the polynucleotide (if present) occurs, and (iv) detecting the presence or absence of an amplification product, or detecting the size of the amplification product and comparing the length to a control sample. It is anticipated that PCR and/or LCR may be desirable to use as a preliminary amplification step in conjunction with any of the techniques used for detecting mutations described herein.

Alternative amplification methods include: self sustained sequence replication [Guatelli, J.C. et al., (47)], transcriptional amplification system [Kwoh, D.Y. et al., (48)], Q-Beta replicase [Lizardi, P.M. et al., (49)], or any other polynucleotide amplification method, followed by the detection of the amplified molecules using techniques well known to those of skill in the art. These detection schemes are especially useful for the detection of polynucleotide molecules if such molecules are present in very low numbers.

In a preferred embodiment of the subject assay, mutations in, or allelic variants, of a gene from a sample cell are identified by alterations in restriction enzyme cleavage patterns. For example, sample and control DNA is isolated, amplified (optionally), digested with one or more restriction endonucleases, and fragment length sizes are determined by gel electrophoresis. Moreover; the use of sequence specific ribozymes (see, for example, U.S. Patent No. 5,498,531) can be used to score for the presence of specific mutations by development or loss of a ribozyme cleavage site.

4. In situ hybridization

In one aspect, the method comprises *in situ* hybridization with a probe derived from a given marker polynucleotide, which sequence is selected from any of the polynucleotide sequences of the SEQ ID NOS:1 to 74 or a sequence complementary thereto. The method comprises contacting the labeled hybridization probe with a sample of a given type of tissue from a patient potentially having cardiovascular disease and arteriosclerosis in particular as well as normal tissue from a person with no cardiovascular disease, and determining whether the probe labels tissue of the patient to a degree significantly different (e.g., by at least a factor of two, or at least a factor of five, or at least a factor of twenty, or at least a factor of fifty) than the degree to which normal tissue is labelled.

5. Immunohistochemistry

Where tissue samples are employed, immunohistochemical staining may be used to determine the number of cells having the marker polypeptide phenotype. For such staining, a multiblock of tissue is taken from the biopsy or other tissue sample and subjected to proteolytic hydrolysis, employing such agents as protease K or pepsin. In certain embodiments, it may be desirable to isolate a nuclear fraction from the sample cells and detect the level of the marker polypeptide in the nuclear fraction.

The tissues samples are fixed by treatment with a reagent such as formalin, glutaraldehyde, methanol, or the like. The samples are then incubated with an antibody, preferably a monoclonal antibody, with binding specificity for the marker polypeptides. This antibody may be conjugated to a Label for subsequent detection of binding. samples are incubated for a time Sufficient for formation of the immuno-complexes. Binding of the antibody is then detected by virtue of a Label conjugated to this antibody. Where the antibody is unlabelled, a second labelled antibody may be employed, e.g., which is specific for the isotype of the anti-marker polypeptide anti-

body. Examples of Labels which may be employed include radionuclides, fluorescens, chemiluminescens, enzymes and such.

Where enzymes are employed, the Substrate for the enzyme may be added to the samples to provide a coloured or fluorescent product. Examples of suitable enzymes for use in conjugates include horseradish peroxidase, alkaline phosphatase, malate dehydrogenase and the like. Where not commercially available, such antibody-enzyme conjugates are readily produced by techniques known to those skilled in the art.

In one embodiment, the assay is performed as a dot blot assay. The dot blot assay finds particular application where tissue samples are employed as it allows determination of the average amount of the marker polypeptide associated with a Single cell by correlating the amount of marker polypeptide in a cell-free extract produced from a predetermined number of cells.

In yet another embodiment, the Invention contemplates using a panel of antibodies which are generated against the marker polypeptides of this invention, which polypeptides are encoded by any of the polynucleotide sequences of the SEQ ID NOS:1 to 74. Such a panel of antibodies may be used as a reliable diagnostic probe for cardiovascular disease. The assay of the present invention comprises contacting a biopsy sample containing cells, e.g., macrophages, with a panel of antibodies to one or more of the encoded products to determine the presence or absence of the marker polypeptides.

The diagnostic methods of the subject invention may also be employed as follow-up to treatment, e.g., quantification of the level of marker polypeptides may be indicative of the effectiveness of current or previously employed therapies for cardiovascular diseases and arteriosclerosis in particular as well as the effect of these therapies upon patient prognosis.

The diagnostic assays described above can be adapted to be used as prognostic assays, as well. Such an application takes advantage of the sensitivity of the assays of the Invention to events which take place at characteristic stages in the progression of plaque generation in case of arteriosclerosis. For example, a given marker gene may be up- or down-regulated at a very early stage, perhaps before the cell is developing into a foam cell, while another marker gene may be characteristically up or down regulated only at a much later stage. Such a method could involve the steps of contacting the mRNA of a test cell with a polynucleotide probe derived from a given marker polynucleotide which is expressed at different characteristic levels in cardiovascular disease tissue cells at different stages of arteriosclerosis progression, and determining the approximate amount of hybridization of the probe to the mRNA of the cell, such amount being an indication of the level of expression of the gene in the cell, and thus an indication of the stage of disease progression of the cell; alternatively, the assay can be carried out with an antibody specific for the gene product of the given marker polynucleotide, contacted with the proteins of the test cell. A battery of such tests will disclose not only the existence of a certain arteriosclerotic plaque, but also will allow the clinician to select the mode of treatment most appropriate for the disease, and to predict the likelihood of success of that treatment.

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The methods of the invention can also be used to follow the clinical course of a given cardiovascular disease predisposition. For example, the assay of the Invention can be applied to a blood sample from a patient; following treatment of the patient for CVD, another blood sample is taken and the test repeated. Successful treatment will result in removal of demonstrate differential expression, characteristic of the cardiovascular disease tissue cells, perhaps approaching or even surpassing normal levels.

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6. Data analysis methods

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Comparison of the expression levels of one or more "CVD genes" with reference expression levels, e.g., expression levels in diseased cells of cardiovascular disease or

in normal counterpart cells, is preferably conducted using computer systems. In one embodiment, expression levels are obtained in two cells and these two sets of expression levels are introduced into a computer system for comparison. In a preferred embodiment, one set of expression levels is entered into a computer system
5 for comparison with values that are already present in the computer system, or in computer-readable form that is then entered into the computer system.

In one embodiment, the invention provides a computer readable form of the gene expression profile data of the invention, or of values corresponding to the level of
10 expression of at least one "CVD gene" in a diseased cell. The values can be mRNA expression levels obtained from experiments, e.g., microarray analysis. The values can also be mRNA levels normalised relative to a reference gene whose expression is constant in numerous cells under numerous conditions, e.g., GAPDH. In other embodiments, the values in the computer are ratios of, or differences between,
15 normalised or non-normalized mRNA levels in different samples.

The gene expression profile data can be in the form of a table, such as an Excel table. The data can be alone, or it can be part of a larger database, e.g., comprising other expression profiles. For example, the expression profile data of the invention can be
20 part of a public database. The computer readable form can be in a computer. In another embodiment, the invention provides a computer displaying the gene expression profile data.

In one embodiment, the invention provides a method for determining the similarity
25 between the level of expression of one or more "CVD genes" in a first cell, e.g., a cell of a subject, and that in a second cell, comprising obtaining the level of expression of one or more "CVD genes" in a first cell and entering these values into a computer comprising a database including records comprising values corresponding to levels of expression of one or more "CVD genes" in a second cell, and processor
30 instructions, e.g., a user interface, capable of receiving a selection of one or more values for comparison purposes with data that is stored in the computer. The

computer may further comprise a means for converting the comparison data into a diagram or chart or other type of output.

5 In another embodiment, values representing expression levels of "CVD genes" are entered into a computer system, comprising one or more databases with reference expression levels obtained from more than one cell. For example, the computer comprises expression data of diseased and normal cells. Instructions are provided to the computer, and the computer is capable of comparing the data entered with the data in the computer to determine whether the data entered is more similar to that of
10 a normal cell or of a diseased cell.

In another embodiment, the computer comprises values of expression levels in cells of subjects at different stages of cardiovascular disease, and the computer is capable of comparing expression data entered into the computer with the data stored, and
15 produce results indicating to which of the expression profiles in the computer, the one entered is most similar, such as to determine the stage of cardiovascular disease in the subject.

In yet another embodiment, the reference expression profiles in the computer are
20 expression profiles from cells of cardiovascular disease of one or more subjects, which cells are treated *in vivo* or *in vitro* with a drug used for therapy of cardiovascular disease. Upon entering of expression data of a cell of a subject treated *in vitro* or *in vivo* with the drug, the computer is instructed to compare the data entered to the data in the computer, and to provide results indicating whether the
25 expression data input into the computer are more similar to those of a cell of a subject that is responsive to the drug or more similar to those of a cell of a subject that is not responsive to the drug. Thus, the results indicate whether the subject is likely to respond to the treatment with the drug or unlikely to respond to it.

30 In one embodiment, the invention provides a system that comprises a means for receiving gene expression data for one or a plurality of genes; a means for comparing

the gene expression data from each of said one or plurality of genes to a common reference frame; and a means for presenting the results of the comparison. This system may further comprise a means for clustering the data.

5 In another embodiment, the invention provides a computer program for analysing gene expression data comprising (i) a computer code that receives as input gene expression data for a plurality of genes and (ii) a computer code that compares said gene expression data from each of said plurality of genes to a common reference frame.

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The invention also provides a machine-readable or computer-readable medium including program instructions for performing the following steps: (i) comparing a plurality of values corresponding to expression levels of one or more genes characteristic of cardiovascular disease in a query cell with a database including records comprising reference expression or expression profile data of one or more reference cells and an annotation of the type of cell; and (ii) indicating to which cell the query cell is most similar based on similarities of expression profiles. The reference cells can be cells from subjects at different stages of cardiovascular disease. The reference cells can also be cells from subjects responding or not responding to a particular drug treatment and optionally incubated *in vitro* or *in vivo* with the drug.

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The reference cells may also be cells from subjects responding or not responding to several different treatments, and the computer system indicates a preferred treatment for the subject. Accordingly, the invention provides a method for selecting a therapy for a patient having cardiovascular disease, the method comprising: (i) providing the level of expression of one or more genes characteristic of cardiovascular disease in a diseased cell of the patient; (ii) providing a plurality of reference profiles, each associated with a therapy, wherein the subject expression profile and each reference profile has a plurality of values, each value representing the level of expression of a gene characteristic of cardiovascular disease; and (iii) selecting the reference profile most similar to the subject expression profile, to thereby select a therapy for said

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patient. In a preferred embodiment step (iii) is performed by a computer. The most similar reference profile may be selected by weighing a comparison value of the plurality using a weight value associated with the corresponding expression data.

5 The relative abundance of an mRNA in two biological samples can be scored as a perturbation and its magnitude determined (i.e., the abundance is different in the two sources of mRNA tested), or as not perturbed (i.e., the relative abundance is the same). In various embodiments, a difference between the two sources of RNA of at least a factor of about 25% (RNA from one source is 25% more abundant in one
10 source than the other source), more usually about 50%, even more often by a factor of about 2 (twice as abundant), 3 (three times as abundant) or 5 (five times as abundant) is scored as a perturbation. Perturbations can be used by a computer for calculating and expression comparisons.

15 Preferably, in addition to identifying a perturbation as positive or negative, it is advantageous to determine the magnitude of the perturbation. This can be carried out, as noted above, by calculating the ratio of the emission of the two fluorophores used for differential labeling, or by analogous methods that will be readily apparent to those of skill in the art.

20 The computer readable medium may further comprise a pointer to a descriptor of a stage of cardiovascular disease or to a treatment for cardiovascular disease.

In operation, the means for receiving gene expression data, the means for comparing
25 the gene expression data, the means for presenting, the means for normalising, and the means for clustering within the context of the systems of the present invention can involve a programmed computer with the respective functionalities described herein, implemented in hardware or hardware and software; a logic circuit or other component of a programmed computer that performs the operations specifically
30 identified herein, dictated by a computer program; or a computer memory encoded

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with executable instructions representing a computer program that can cause a computer to function in the particular fashion described herein.

5 Those skilled in the art will understand that the systems and methods of the present invention may be applied to a variety of systems, including IBM-compatible personal computers running MS-DOS or Microsoft Windows.

10 The computer may have internal components linked to external components. The internal components may include a processor element interconnected with a main memory. The computer system can be an Intel Pentium®-based processor of 200 MHz or greater clock rate and with 32 MB or more of main memory. The external component may comprise a mass storage, which can be one or more hard disks (which are typically packaged together with the processor and memory). Such hard disks are typically of 1 GB or greater storage capacity. Other external components
15 include a user interface device, which can be a monitor, together with an inputting device, which can be a "mouse", or other graphic input devices, and/or a keyboard. A printing device can also be attached to the computer.

20 Typically, the computer system is also linked to a network link, which can be part of an Ethernet link to other local computer systems, remote computer systems, or wide area communication networks, such as the Internet. This network link allows the computer system to share data and processing tasks with other computer systems.

25 Loaded into memory during operation of this system are several software components, which are both standard in the art and special to the instant invention. These software components collectively cause the computer system to function according to the methods of this invention. These software components are typically stored on a mass storage. A software component represents the operating system, which is responsible for managing the computer system and its network
30 interconnections. This operating system can be, for example, of the Microsoft Windows' family, such as Windows 95, Windows 98, or Windows NT. A software

component represents common languages and functions conveniently present on this system to assist programs implementing the methods specific to this invention. Many high or low level computer languages can be used to program the analytic methods of this invention. Instructions can be interpreted during run-time or
5 compiled. Preferred languages include C/C++, and JAVA[®]. Most preferably, the methods of this invention are programmed in mathematical software packages which allow symbolic entry of equations and high-level specification of processing, including algorithms to be used, thereby freeing a user of the need to procedurally
10 program individual equations or algorithms. Such packages include Matlab from Mathworks (Natick, Mass.), Mathematica from Wolfram Research (Champaign, Ill.), or S-Plus from Math Soft (Cambridge, Mass.). Accordingly, a software component represents the analytic methods of this invention as programmed in a procedural language or symbolic package. In a preferred embodiment, the computer system also contains a database comprising values representing levels of expression of one or
15 more genes characteristic of cardiovascular disease. The database may contain one or more expression profiles of genes characteristic of cardiovascular disease in different cells.

In an exemplary implementation, to practice the methods of the present invention, a
20 user first loads expression profile data into the computer system. These data can be directly entered by the user from a monitor and keyboard, or from other computer systems linked by a network connection, or on removable storage media such as a CD-ROM or floppy disk or through the network. Next the user causes execution of expression profile analysis software which performs the steps of comparing and, e.g.,
25 clustering co-varying genes into groups of genes.

In another exemplary implementation, expression profiles are compared using a method described in U.S. Patent No. 6,203,987. A user first loads expression profile data into the computer system. Geneset profile definitions are loaded into the
30 memory from the storage media or from a remote computer, preferably from a dynamic geneset database system, through the network. Next the user causes

execution of projection software which performs the steps of converting expression profile to projected expression profiles. The projected expression profiles are then displayed.

- 5 In yet another exemplary implementation, a user first loads a projected profile into the memory. The user then causes the loading of a reference profile into the memory. Next, the user causes the execution of comparison software which performs the steps of objectively comparing the profiles.

10 Antisense oligonucleotides

Antisense oligonucleotides are nucleotide sequences which are complementary to a specific DNA or RNA sequence. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form complexes
15 and block either transcription or translation. Preferably, an antisense oligonucleotide is at least 6 nucleotides in length, but can be at least 7, 8, 10, 12, 15, 20, 25, 30, 35, 40, 45, or 50 or more nucleotides long. Longer sequences also can be used. Antisense oligonucleotide molecules can be provided in a DNA construct and introduced into a cell as described above to decrease the level of „CVD gene“ gene products in the
20 cell.

Antisense oligonucleotides can be deoxyribonucleotides, ribonucleotides, peptide nucleic acids (PNAs; described in U.S. Pat. No. 5,714,331), locked nucleic acids (LNAs; described in WO 99/12826), or a combination of them. Oligonucleotides can
25 be synthesised manually or by an automated synthesiser, by covalently linking the 5' end of one nucleotide with the 3' end of another nucleotide with non-phosphodiester internucleotide linkages such as alkylphosphonates, phosphorothioates, phosphorodithioates, alkylphosphonothioates, alkylphosphonates, phosphoramidates, phosphate esters, carbamates, acetamidate, carboxymethyl esters, carbonates, and phosphate
30 triesters. See Brown, (50); Sonveaux, (51) and Uhlmann et al., (52).

Modifications of „CVD gene“ expression can be obtained by designing antisense oligonucleotides which will form duplexes to the control, 5', or regulatory regions of the „CVD gene“. Oligonucleotides derived from the transcription initiation site, e.g., between positions 10 and +10 from the start site, are preferred. Similarly, inhibition
5 can be achieved using "triple helix" base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or chaperons. Therapeutic advances using triplex DNA have been described in the literature [e.g., Gee et al., (53)]. An antisense oligonucleotide also can be designed to block
10 translation of mRNA by preventing the transcript from binding to ribosomes.

Precise complementarity is not required for successful complex formation between an antisense oligonucleotide and the complementary sequence of a „CVD gene“ polynucleotide. Antisense oligonucleotides which comprise, for example, 2, 3, 4, or 5
15 or more stretches of contiguous nucleotides which are precisely complementary to a „CVD gene“ polynucleotide, each separated by a stretch of contiguous nucleotides which are not complementary to adjacent „CVD gene“ nucleotides, can provide sufficient targeting specificity for „CVD gene“ mRNA. Preferably, each stretch of complementary contiguous nucleotides is at least 4, 5, 6, 7, or 8 or more nucleotides
20 in length. Non-complementary intervening sequences are preferably 1, 2, 3, or 4 nucleotides in length. One skilled in the art can easily use the calculated melting point of an antisense-sense pair to determine the degree of mismatching which will be tolerated between a particular antisense oligonucleotide and a particular „CVD gene“ polynucleotide sequence.

25 Antisense oligonucleotides can be modified without affecting their ability to hybridise to a „CVD gene“ polynucleotide. These modifications can be internal or at one or both ends of the antisense molecule. For example, internucleoside phosphate linkages can be modified by adding cholesteryl or diamine moieties with varying
30 numbers of carbon residues between the amino groups and terminal ribose. Modified bases and/or sugars, such as arabinose instead of ribose, or a 3', 5' substituted

oligonucleotide in which the 3' hydroxyl group or the 5' phosphate group are substituted, also can be employed in a modified antisense oligonucleotide. These modified oligonucleotides can be prepared by methods well known in the art. See, e.g., Agrawal et al., (54); Uhlmann et al., (52) and Uhlmann et al., (55).

5

Ribozymes

Ribozymes are RNA molecules with catalytic activity. See, e.g., Cech, (56); 1987; Cech, (57) and Couture & Stinchcomb, (58). Ribozymes can be used to inhibit gene
10 function by cleaving an RNA sequence, as is known in the art (e.g., Haseloff et al., U.S. Patent 5,641,673). The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. Examples include engineered hammerhead motif ribozyme molecules that can specifically and efficiently catalyze endonucleo-
15 lytic cleavage of specific nucleotide sequences.

The transcribed sequence of a „CVD gene“ can be used to generate ribozymes which will specifically bind to mRNA transcribed from a „CVD gene“ genomic locus. Methods of designing and constructing ribozymes which can cleave other RNA
20 molecules in trans in a highly sequence specific manner have been developed and described in the art [see Haseloff et al., (59)]. For example, the cleavage activity of ribozymes can be targeted to specific RNAs by engineering a discrete "hybridization" region into the ribozyme. The hybridization region contains a sequence complementary to the target RNA and thus specifically hybridises with the target
25 (see, for example, Gerlach et al., EP No. 0 321201).

Specific ribozyme cleavage sites within a „CVD gene“ RNA target can be identified by scanning the target molecule for ribozyme cleavage sites which include the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences
30 of between 15 and 20 ribonucleotides corresponding to the region of the target RNA containing the cleavage site can be evaluated for secondary structural features which

may render the target inoperable. Suitability of candidate „CVD gene“ RNA targets also can be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays. Longer complementary sequences can be used to increase the affinity of the hybridization sequence for the target. The hybridising and cleavage regions of the ribozyme can be integrally related such that upon hybridising to the target RNA through the complementary regions, the catalytic region of the ribozyme can cleave the target.

Ribozymes can be introduced into cells as part of a DNA construct. Mechanical methods, such as microinjection, liposome-mediated transfection, electroporation, or calcium phosphate precipitation, can be used to introduce a ribozyme-containing DNA construct into cells in which it is desired to decrease „CVD gene“ expression. Alternatively, if it is desired that the cells stably retain the DNA construct, the construct can be supplied on a plasmid and maintained as a separate element or integrated into the genome of the cells, as is known in the art. A ribozyme-encoding DNA construct can include transcriptional regulatory elements, such as a promoter element, an enhancer or UAS element, and a transcriptional terminator signal, for controlling transcription of ribozymes in the cells.

As taught in Haseloff et al., U.S. Pat. No. 5,641,673, ribozymes can be engineered so that ribozyme expression will occur in response to factors which induce expression of a target gene. Ribozymes also can be engineered to provide an additional level of regulation, so that destruction of mRNA occurs only when both a ribozyme and a target gene are induced in the cells.

Polypeptide detection

The subject invention further provides a method of determining whether a cell sample obtained from a subject possesses an abnormal amount of marker polypeptide which comprises (a) obtaining a cell sample from the subject, (b) quantitatively determining the amount of the marker polypeptide in the sample so obtained, and (c)

comparing the amount of the marker polypeptide so determined with a known standard, so as to thereby determine whether the cell sample obtained from the subject possesses an abnormal amount of the marker polypeptide. Such marker polypeptides may be detected by immunohistochemical assays, dot-blot assays, ELISA and the like.

Antibodies

Any type of antibody known in the art can be generated to bind specifically to an epitope of a „CVD gene“ polypeptide. An antibody as used herein includes intact immunoglobulin molecules, as well as fragments thereof, such as Fab, F(ab)₂, and Fv, which are capable of binding an epitope of a „CVD gene“ polypeptide. Typically, at least 6, 8, 10, or 12 contiguous amino acids are required to form an epitope. However, epitopes which involve non-contiguous amino acids may require more, e.g., at least 15, 25, or 50 amino acids.

An antibody which specifically binds to an epitope of a „CVD gene“ polypeptide can be used therapeutically, as well as in immunochemical assays, such as Western blots, ELISAs, radioimmunoassays, immunohistochemical assays, immunoprecipitations, or other immunochemical assays known in the art. Various immunoassays can be used to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays are well known in the art. Such immunoassays typically involve the measurement of complex formation between an immunogen and an antibody which specifically binds to the immunogen.

Typically, an antibody which specifically binds to a „CVD gene“ polypeptide provides a detection signal at least 5-, 10-, or 20-fold higher than a detection signal provided with other proteins when used in an immunochemical assay. Preferably, antibodies which specifically bind to „CVD gene“ polypeptides do not detect other proteins in immunochemical assays and can immunoprecipitate a „CVD gene“ polypeptide from solution.

„CVD gene“ polypeptides can be used to immunize a mammal, such as a mouse, rat, rabbit, guinea pig, monkey, or human, to produce polyclonal antibodies. If desired, a „CVD gene“ polypeptide can be conjugated to a carrier protein, such as bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin. Depending on the host species, various adjuvants can be used to increase the immunological response. Such adjuvants include, but are not limited to, Freund's adjuvant, mineral gels (e.g., aluminum hydroxide), and surface active substances (e.g. lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, keyhole limpet hemocyanin, and dinitrophenol). Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and *Corynebacterium parvum* are especially useful.

Monoclonal antibodies which specifically bind to a „CVD gene“ polypeptide can be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These techniques include, but are not limited to, the hybridoma technique, the human B cell hybridoma technique, and the EBV hybridoma technique [Kohler et al., (60); Kozbor et al., (61); Cote et al., (62) and Cole et al., (63)].

In addition, techniques developed for the production of chimeric antibodies, the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used [Morrison et al., (64); Neuberger et al., (65); Takeda et al., (66)]. Monoclonal and other antibodies also can be humanized to prevent a patient from mounting an immune response against the antibody when it is used therapeutically. Such antibodies may be sufficiently similar in sequence to human antibodies to be used directly in therapy or may require alteration of a few key residues. Sequence differences between rodent antibodies and human sequences can be minimized by replacing residues which differ from those in the human sequences by site directed mutagenesis of individual residues or by grafting of entire complementarity determining regions. Alternatively, humanized antibodies can be produced using recombinant methods, as described in

GB2188638B. Antibodies which specifically bind to a „CVD gene“ polypeptide can contain antigen binding sites which are either partially or fully humanized, as disclosed in U.S. Patent 5,565,332.

5 Alternatively, techniques described for the production of single chain antibodies can be adapted using methods known in the art to produce single chain antibodies which specifically bind to „CVD gene“ polypeptides. Antibodies with related specificity, but of distinct idiotypic composition, can be generated by chain shuffling from random combinatorial immunoglobulin libraries [Burton, (67)].

10

Single-chain antibodies also can be constructed using a DNA amplification method, such as PCR, using hybridoma cDNA as a template [Thirion et al., (68)]. Single-chain antibodies can be mono- or bispecific, and can be bivalent or tetravalent. Construction of tetravalent, bispecific single-chain antibodies is taught, for example, in Coloma & Morrison, (69). Construction of bivalent, bispecific single-chain antibodies is taught in Mallender & Voss, (70).

15

A nucleotide sequence encoding a single-chain antibody can be constructed using manual or automated nucleotide synthesis, cloned into an expression construct using standard recombinant DNA methods, and introduced into a cell to express the coding sequence, as described below. Alternatively, single-chain antibodies can be produced directly using, for example, filamentous phage technology [Verhaar et al., (71); Nicholls et al., (72)].

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25 Antibodies which specifically bind to „CVD gene“ polypeptides also can be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature [Orlandi et al., (73) and Winter et al., (74)].

30 Other types of antibodies can be constructed and used therapeutically in methods of the invention. For example, chimeric antibodies can be constructed as disclosed in

WO 93/03151. Binding proteins which are derived from immunoglobulins and which are multivalent and multispecific, such as the antibodies described in WO 94/13804, also can be prepared.

5 Antibodies according to the invention can be purified by methods well known in the art. For example, antibodies can be affinity purified by passage over a column to which a „CVD gene“ polypeptide is bound. The bound antibodies can then be eluted from the column using a buffer with a high salt concentration.

10 Immunoassays are commonly used to quantify the levels of proteins in cell samples, and many other immunoassay techniques are known in the art. The invention is not limited to a particular assay procedure, and therefore is intended to include both homogeneous and heterogeneous procedures. Exemplary immunoassays which can be conducted according to the invention include fluorescence polarisation
15 immunoassay (FPIA), fluorescence immunoassay (FIA), enzyme immunoassay (ELA), nephelometric inhibition immunoassay (NIA), enzyme linked immunosorbent assay (ELISA), and radioimmunoassay (RIA). An indicator moiety, or label group, can be attached to the subject antibodies and is selected so as to meet the needs of various uses of the method which are often dictated by the availability of assay
20 equipment and compatible immunoassay procedures. General techniques to be used in performing the various immunoassays noted above are known to those of ordinary skill in the art.

25 In another embodiment, the level of the encoded product, i.e., the product encoded by any of the polynucleotide sequences of the SEQ ID NOS:1 to 74 or a sequence complementary thereto, in a biological fluid (e.g., blood or urine) of a patient may be determined as a way of monitoring the level of expression of the marker polynucleotide sequence in cells of that patient. Such a method would include the steps of obtaining a sample of a biological fluid from the patient, contacting the
30 sample (or proteins from the sample) with an antibody specific for a encoded marker polypeptide, and determining the amount of immune complex formation by the

antibody, with the amount of immune complex formation being indicative of the level of the marker encoded product in the sample. This determination is particularly instructive when compared to the amount of immune complex formation by the same antibody in a control sample taken from a normal individual or in one or more
5 samples previously or subsequently obtained from the same person.

In another embodiment, the method can be used to determine the amount of marker polypeptide present in a cell, which in turn can be correlated with progression of the disorder, e.g., plaque formation. The level of the marker polypeptide can be used
10 predictively to evaluate whether a sample of cells contains cells which are, or are predisposed towards becoming, plaque associated cells. The observation of marker polypeptide level can be utilized in decisions regarding, e.g., the use of more stringent therapies.

As set out above, one aspect of the present invention relates to diagnostic assays for determining, in the context of cells isolated from a patient, if the level of a marker polypeptide is significantly reduced in the sample cells. The term "significantly reduced" refers to a cell phenotype wherein the cell possesses a reduced cellular amount of the marker polypeptide relative to a normal cell of similar tissue origin.
15 For example, a cell may have less than about 50%, 25%, 10%, or 5% of the marker polypeptide that a normal control cell. In particular, the assay evaluates the level of marker polypeptide in the test cells, and, preferably, compares the measured level with marker polypeptide detected in at least one control cell, e.g., a normal cell and/or a transformed cell of known phenotype.
20

Of particular importance to the subject invention is the ability to quantify the level of marker polypeptide as determined by the number of cells associated with a normal or abnormal marker polypeptide level. The number of cells with a particular marker polypeptide phenotype may then be correlated with patient prognosis. In one
25 embodiment of the invention, the marker polypeptide phenotype of the lesion is determined as a percentage of cells in a biopsy which are found to have abnormally
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high/low levels of the marker polypeptide. Such expression may be detected by immunohistochemical assays, dot-blot assays, ELISA and the like.

Polypeptide activity

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In one embodiment the present invention provides a method for screening potentially therapeutic agents which modulate the activity of one or more "CVD gene" polypeptides, such that if the activity of the polypeptide is increased as a result of the upregulation of the "CVD gene" in a subject having or at risk for cardiovascular disease and arteriosclerosis in particular, the therapeutic substance will decrease the activity of the polypeptide relative to the activity of the same polypeptide in a subject not having or not at risk for cardiovascular diseases or arteriosclerosis in particular but not treated with the therapeutic agent. Likewise, if the activity of the polypeptide as a result of the downregulation of the "CVD gene" is decreased in a subject having or at risk for cardiovascular disease or arteriosclerosis in particular, the therapeutic agent will increase the activity of the polypeptide relative to the activity of the same polypeptide in a subject not having or not at risk for cardiovascular disease or arteriosclerosis in particular, but not treated with the therapeutic agent.

20 The activity of the "CVD gene" polypeptides indicated in Table 4 may be measured by any means known to those of skill in the art, and which are particular for the type of activity performed by the particular polypeptide. Examples of specific assays which may be used to measure the activity of particular polynucleotides are shown below.

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a) G protein coupled receptors

In one embodiment, the "CVD gene" polynucleotide may encode a G protein coupled receptor. In one embodiment, the present invention provides a method of screening potential modulators (inhibitors or activators) of the G protein coupled receptor by

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measuring changes in the activity of the receptor in the presence of a candidate modulator.

1. G_i -coupled receptors

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Cells (such as CHO cells or primary cells) are stably transfected with the relevant receptor and with an inducible CRE-luciferase construct. Cells are grown in 50% Dulbecco's modified Eagle medium / 50% F12 (DMEM/F12) supplemented with 10% FBS, at 37°C in a humidified atmosphere with 10% CO₂ and are routinely split at a ratio of 1:10 every 2 or 3 days. Test cultures are seeded into 384 - well plates at an appropriate density (e.g. 2000 cells / well in 35 µl cell culture medium) in DMEM/F12 with FBS, and are grown for 48 hours (range: ~ 24 - 60 hours, depending on cell line). Growth medium is then exchanged against serum free medium (SFM; e.g. Ultra-CHO), containing 0,1% BSA. Test compounds dissolved in DMSO are diluted in SFM and transferred to the test cultures (maximal final concentration 10 µmolar), followed by addition of forskolin (~ 1 µmolar, final conc.) in SFM + 0,1% BSA 10 minutes later. In case of antagonist screening both, an appropriate concentration of agonist, and forskolin are added. The plates are incubated at 37°C in 10% CO₂ for 3 hours. Then the supernatant is removed, cells are lysed with lysis reagent (25 mmolar phosphate-buffer, pH 7,8 , containing 2 mmolar DDT, 10% glycerol and 3% Triton X100). The luciferase reaction is started by addition of substrate-buffer (e.g. luciferase assay reagent, Promega) and luminescence is immediately determined (e.g. Berthold luminometer or Hamamatsu camera system).

25

2. G_s -coupled receptors

Cells (such as CHO cells or primary cells) are stably transfected with the relevant receptor and with an inducible CRE-luciferase construct. Cells are grown in 50% Dulbecco's modified Eagle medium / 50% F12 (DMEM/F12) supplemented with 10% FBS, at 37°C in a humidified atmosphere with 10% CO₂ and are routinely split

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at a ratio of 1:10 every 2 or 3 days. Test cultures are seeded into 384 – well plates at an appropriate density (e.g. 1000 or 2000 cells / well in 35 µl cell culture medium) in DMEM/F12 with FBS, and are grown for 48 hours (range: ~ 24 - 60 hours, depending on cell line). The assay is started by addition of test-compounds in serum free medium (SFM; e.g. Ultra-CHO) containing 0,1% BSA: Test compounds are dissolved in DMSO, diluted in SFM and transferred to the test cultures (maximal final concentration 10 µmolar, DMSO conc. < 0,6 %). In case of antagonist screening an appropriate concentration of agonist is added 5 – 10 minutes later. The plates are incubated at 37°C in 10% CO₂ for 3 hours. Then the cells are lysed with 10 µl lysis reagent per well (25 mmolar phosphate-buffer, pH 7,8 , containing 2 mmolar DDT, 10% glycerol and 3% Triton X100) and the luciferase reaction is started by addition of 20 µl substrate-buffer per well (e.g. luciferase assay reagent, Promega). Measurement of luminescence is started immediately (e.g. Berthold luminometer or Hamamatzu camera system).

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3. G_q-coupled receptors

Cells (such as CHO cells or primary cells) are stably transfected with the relevant receptor. Cells expressing functional receptor protein are grown in 50% Dulbecco's modified Eagle medium / 50% F12 (DMEM/F12) supplemented with 10% FBS, at 37°C in a humidified atmosphere with 5% CO₂ and are routinely split at a cell line dependent ratio every 3 or 4 days. Test cultures are seeded into 384 – well plates at an appropriate density (e.g. 2000 cells / well in 35 µl cell culture medium) in DMEM/F12 with FBS, and are grown for 48 hours (range: ~ 24 - 60 hours, depending on cell line). Growth medium is then exchanged against physiological salt solution (e.g. Tyrode solution). Test compounds dissolved in DMSO are diluted in Tyrode solution containing 0.1% BSA and transferred to the test cultures (maximal final concentration 10 µmolar). After addition of the receptor specific agonist the

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resulting Gq-mediated intracellular calcium increase is measured using appropriate read-out systems (e.g. calcium-sensitive dyes).

b) Ion channels

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Ion channels are integral membrane proteins involved in electrical signaling, transmembrane signal transduction, and electrolyte and solute transport. By forming macromolecular pores through the membrane lipid bilayer, ion channels account for the flow of specific ion species driven by the electrochemical potential gradient for the permeating ion. At the single molecule level, individual channels undergo conformational transitions ("gating") between the 'open' (ion conducting) and 'closed' (non conducting) state. Typical single channel openings last for a few milliseconds and result in elementary transmembrane currents in the range of 10^{-9} - 10^{-12} Ampere. Channel gating is controlled by various chemical and/or biophysical parameters, such as neurotransmitters and intracellular second messengers ('ligand-gated' channels) or membrane potential ('voltage-gated' channels). Ion channels are functionally characterised by their ion selectivity, gating properties, and regulation by hormones and pharmacological agents. Because of their central role in signaling and transport processes, ion channels present ideal targets for pharmacological therapeutics in various pathophysiological settings.

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Screening for compounds interacting with ion channels to either inhibit or promote their activity can be based on (1.) binding and (2.) functional assays in living cells (110).

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In one embodiment, the "CVD gene" may encode an ion channel. In one embodiment, the present invention provides a method of screening potential activators or inhibitors of channels activity of the "CVD gene" polypeptide. Screening for compounds interaction with ion channels to either inhibit or promote their activity can be based on (1.) binding and (2.) functional assays in living cells. See e.g. Hille (110).

1. For ligand-gated channels, e.g. ionotropic neurotransmitter/hormone receptors, assays can be designed detecting binding to the target by competition between the compound and a labeled ligand.
- 5 2. Ion channel function can be tested functionally in living cells. Target proteins are either expressed endogenously in appropriate reporter cells or are introduced recombinantly. Channel activity can be monitored by (2.1) concentration changes of the permeating ion (most prominently Ca^{2+} ions), (2.2) by changes in the transmembrane electrical potential gradient, and (2.3) by measuring a cellular response (e.g. expression of a reporter gene, secretion of a neurotransmitter) triggered or modulated by the target activity.
- 10 2.1 Channel activity results in transmembrane ion fluxes. Thus activation of ionic channels can be monitored by the resulting changes in intracellular ion concentrations using luminescent or fluorescent indicators. Because of its wide dynamic range and availability of suitable indicators this applies particularly to changes in intracellular Ca^{2+} ion concentration ($[\text{Ca}^{2+}]_i$). $[\text{Ca}^{2+}]_i$ can be measured, for example, by aequorin luminescence or fluorescence dye technology (e.g. using Fluo-3, Indo-1, Fura-2). Cellular assays can be designed where either the Ca^{2+} flux through the target channel itself is measured directly or where modulation of the target channel affects membrane potential and thereby the activity of co-expressed voltage-gated Ca^{2+} channels.
- 15 2.2 Ion channel currents result in changes of electrical membrane potential (V_m) which can be monitored directly using potentiometric fluorescent probes. These electrically charged indicators (e.g. the anionic oxonol dye DiBAC₄(3)) redistribute between extra- and intracellular compartment in response to voltage changes. The equilibrium distribution is governed by the Nernst-equation. Thus changes in membrane potential results in concomitant changes in cellular fluorescence. Again, changes in V_m might be caused directly by the activity of the target ion channel or through amplification and/or prolongation of the signal by channels co-expressed in the same cell.
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- 25
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2.3 Target channel activity can cause cellular Ca^{2+} entry either directly or through activation of additional Ca^{2+} channel (see 2.1). The resulting intracellular Ca^{2+} signals regulate a variety of cellular responses, e.g. secretion or gene transcription. Therefore modulation of the target channel can be detected by monitoring secretion of a known hormone/transmitter from the target-expressing cell or through expression of a reporter gene (e.g. luciferase) controlled by an Ca^{2+} -responsive promoter element (e.g. cyclic AMP/ Ca^{2+} -responsive elements; CRE).

10 c) DNA-binding proteins and transcription factors

In one embodiment, the "CVD gene" may encode a DNA-binding protein or a transcription factor. The activity of such a DNA-binding protein or a transcription factor may be measured, for example, by a promoter assay which measures the ability of the DNA-binding protein or the transcription factor to initiate transcription of a test sequence linked to a particular promoter. In one embodiment, the present invention provides a method of screening test compounds for its ability to modulate the activity of such a DNA-binding protein or a transcription factor by measuring the changes in the expression of a test gene which is regulated by a promoter which is responsive to the transcription factor.

Promoter assays

A promoter assay was set up with a human hepatocellular carcinoma cell HepG2 that was stably transfected with a luciferase gene under the control of a gene of interest (e.g. thyroid hormone) regulated promoter. The vector 2xIROluc, which was used for transfection, carries a thyroid hormone responsive element (TRE) of two 12 bp inverted palindromes separated by an 8 bp spacer in front of a tk minimal promoter and the luciferase gene. Test cultures were seeded in 96 well plates in serum - free Eagle's Minimal Essential Medium supplemented with glutamine, tricine, sodium pyruvate, non - essential amino acids, insulin, selen, transferrin, and were cultivated

in a humidified atmosphere at 10 % CO₂ at 37°C. After 48 hours of incubation serial dilutions of test compounds or reference compounds (L-T3, L-T4 e.g.) and costimulator if appropriate (final concentration 1 nM) were added to the cell cultures and incubation was continued for the optimal time (e.g. another 4-72 hours). The cells were then lysed by addition of buffer containing Triton X100 and luciferin and the luminescence of luciferase induced by T3 or other compounds was measured in a luminometer. For each concentration of a test compound replicates of 4 were tested. EC₅₀ – values for each test compound were calculated by use of the Graph Pad Prism Scientific software.

Screening Methods

The invention provides assays for screening test compounds which bind to or modulate the activity of a „CVD gene“ polypeptide or a „CVD gene“ polynucleotide. A test compound preferably binds to a „CVD gene“ polypeptide or polynucleotide. More preferably, a test compound decreases or increases „CVD gene“ activity by at least about 10, preferably about 50, more preferably about 75, 90, or 100% relative to the absence of the test compound.

1. Test Compounds

Test compounds can be pharmacological agents already known in the art or can be compounds previously unknown to have any pharmacological activity. The compounds can be naturally occurring or designed in the laboratory. They can be isolated from microorganisms, animals, or plants, and can be produced recombinant, or synthesised by chemical methods known in the art. If desired, test compounds can be obtained using any of the numerous combinatorial library methods known in the art, including but not limited to, biological libraries, spatially addressable parallel solid phase or solution phase libraries, synthetic library methods requiring deconvolution, the one-bead one-compound library method, and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to

polypeptide, non-peptide oligomer, or small molecule libraries of compounds. [For review see Lam, (75)].

Methods for the synthesis of molecular libraries are well known in the art [see, for example, DeWitt et al., (76); Erb et al., (77); Zuckermann et al., (78); Cho et al., (79); Carell et al., (80) and Gallop et al., (81). Libraries of compounds can be presented in solution [see, e.g., Houghten, (82)], or on beads [Lam, (83)], chips [Fodor, (84)], bacteria or spores (Ladner, U.S. Patent 5,223,409), plasmids [Cull et al., (85)], or phage [Scott & Smith, (86); Devlin, (87); Cwirla et al., (88); Felici, (89)].

High Throughput Screening

Test compounds can be screened for the ability to bind to „CVD gene“ polypeptides or polynucleotides or to affect „CVD gene“ activity or „CVD gene“ expression using high throughput screening. Using high throughput screening, many discrete compounds can be tested in parallel so that large numbers of test compounds can be quickly screened. The most widely established techniques utilize 96-well microtiter plates. The wells of the microtiter plates typically require assay volumes that range from 50 to 500 µl. In addition to the plates, many instruments, materials, pipettors, robotics, plate washers, and plate readers are commercially available to fit the 96-well format.

Alternatively, free format assays, or assays that have no physical barrier between samples, can be used. For example, an assay using pigment cells (melanocytes) in a simple homogeneous assay for combinatorial peptide libraries is described by Jayawickreme et al., (90). The cells are placed under agarose in culture dishes, then beads that carry combinatorial compounds are placed on the surface of the agarose. The combinatorial compounds are partially released the compounds from the beads.

Active compounds can be visualised as dark pigment areas because, as the compounds diffuse locally into the gel matrix, the active compounds cause the cells to change colours.

5 Another example of a free format assay is described by Chelsky, (91), reported at the First Annual Conference of The Society for Biomolecular Screening in Philadelphia, (1995). Chelsky placed a simple homogenous enzyme assay for carbonic anhydrase inside an agarose gel such that the enzyme in the gel would cause a colour change throughout the gel. Thereafter, beads carrying combinatorial compounds via a photo-
10 linker were placed inside the gel and the compounds were partially released by UV light. Compounds that inhibited the enzyme were observed as local zones of inhibition having less colour change.

Yet another example is described by Salmon et al., (92). In this example, combinatorial libraries were screened for compounds that had cytotoxic effects on
15 cancer cells growing in agar.

Another high throughput screening method is described in Beutel et al., U.S. Patent 5,976,813. In this method, test samples are placed in a porous matrix. One or more assay components are then placed within, on top of, or at the bottom of a matrix such
20 as a gel, a plastic sheet, a filter, or other form of easily manipulated solid support. When samples are introduced to the porous matrix they diffuse sufficiently slowly, such that the assays can be performed without the test samples running together.

Binding Assays

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For binding assays, the test compound is preferably a small molecule which binds to and occupies, for example, the ATP/GTP binding site of the enzyme or the active site of a „CVD gene“ polypeptide, such that normal biological activity is prevented. Examples of such small molecules include, but are not limited to, small peptides or
30 peptide-like molecules.

In binding assays, either the test compound or a „CVD gene“ polypeptide can comprise a detectable label, such as a fluorescent, radioisotopic, chemiluminescent, or enzymatic label, such as horseradish peroxidase, alkaline phosphatase, or luciferase. Detection of a test compound which is bound to a „CVD gene“ polypeptide can then be accomplished, for example, by direct counting of radioemmission, by scintillation counting, or by determining conversion of an appropriate substrate to a detectable product.

Alternatively, binding of a test compound to a „CVD gene“ polypeptide can be determined without labeling either of the interactants. For example, a microphysiometer can be used to detect binding of a test compound with a „CVD gene“ polypeptide. A microphysiometer (e.g., CytosensorJ) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between a test compound and a „CVD gene“ polypeptide [McConnell et al., (93)].

Determining the ability of a test compound to bind to a „CVD gene“ polypeptide also can be accomplished using a technology such as real-time Bimolecular Interaction Analysis (BIA) [Sjolander & Urbaniczky, (94), and Szabo et al., (95)]. BIA is a technology for studying biospecific interactions in real time, without labeling any of the interactants (e.g., BIAcoreTM). Changes in the optical phenomenon surface plasmon resonance (SPR) can be used as an indication of real-time reactions between biological molecules.

In yet another aspect of the invention, a „CVD gene“ polypeptide can be used as a "bait protein" in a two-hybrid assay or three-hybrid assay (see, e.g., U.S. Patent 5,283,317; Zervos et al., (96); Madura et al., (97); Bartel et al., (98); Iwabuchi et al., (99) and Brent WO 94/10300), to identify other proteins which bind to or interact with the „CVD gene“ polypeptide and modulate its activity.

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The two-hybrid system is based on the modular nature of most transcription factors, which consist of separable DNA-binding and activation domains. Briefly, the assay utilizes two different DNA constructs. For example, in one construct, polynucleotide encoding a „CVD gene“ polypeptide can be fused to a polynucleotide encoding the DNA binding domain of a known transcription factor (e.g., GAL4). In the other construct a DNA sequence that encodes an unidentified protein ("prey" or "sample") can be fused to a polynucleotide that codes for the activation domain of the known transcription factor. If the "bait" and the "prey" proteins are able to interact in vivo to form an protein- dependent complex, the DNA-binding and activation domains of the transcription factor are brought into close proximity. This proximity allows transcription of a reporter gene (e.g., LacZ), which is operably linked to a transcriptional regulatory site responsive to the transcription factor. Expression of the reporter gene can be detected, and cell colonies containing the functional transcription factor can be isolated and used to obtain the DNA sequence encoding the protein which interacts with the „CVD gene“ polypeptide.

It may be desirable to immobilise either a „CVD gene“ polypeptide (or polynucleotide) or the test compound to facilitate separation of bound from unbound forms of one or both of the interactants, as well as to accommodate automation of the assay. Thus, either a „CVD gene“ polypeptide (or polynucleotide) or the test compound can be bound to a solid support. Suitable solid supports include, but are not limited to, glass or plastic slides, tissue culture plates, microtiter wells, tubes, silicon chips, or particles such as beads (including, but not limited to, latex, polystyrene, or glass beads). Any method known in the art can be used to attach a „CVD gene“ polypeptide (or polynucleotide) or test compound to a solid support, including use of covalent and non-covalent linkages, passive absorption, or pairs of binding moieties attached respectively to the polypeptide (or polynucleotide) or test compound and the solid support. Test compounds are preferably bound to the solid support in an array, so that the location of individual test compounds can be tracked. Binding of a test compound to a „CVD gene“ polypeptide (or polynucleotide) can be

accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtiter plates, test tubes, and microcentrifuge tubes.

5 In one embodiment, a „CVD gene“ polypeptide is a fusion protein comprising a domain that allows the „CVD gene“ polypeptide to be bound to a solid support. For example, glutathione S-transferase fusion proteins can be adsorbed onto glutathione sepharose beads (Sigma Chemical, St. Louis, Mo.) or glutathione derivatized microtiter plates, which are then combined with the test compound or the test compound and the nonadsorbed „CVD gene“ polypeptide; the mixture is then
10 incubated under conditions conducive to complex formation (e.g., at physiological conditions for salt and pH). Following incubation, the beads or microtiter plate wells are washed to remove any unbound components. Binding of the interactants can be determined either directly or indirectly, as described above. Alternatively, the complexes can be dissociated from the solid support before binding is determined.

15 Other techniques for immobilising proteins or polynucleotides on a solid support also can be used in the screening assays of the invention. For example, either a „CVD gene“ polypeptide (or polynucleotide) or a test compound can be immobilized utilizing conjugation of biotin and streptavidin. Biotinylated „CVD gene“ polypeptides (or polynucleotides) or test compounds can be prepared from biotin
20 NHS (N-hydroxysuccinimide) using techniques well known in the art (e.g., biotinylation kit, Pierce Chemicals, Rockford, Ill.) and immobilized in the wells of streptavidin-coated 96 well plates (Pierce Chemical). Alternatively, antibodies which specifically bind to a „CVD gene“ polypeptide, polynucleotide, or a test compound, but which do not interfere with a desired binding site, such as the ATP/GTP binding
25 site or the active site of the „CVD gene“ polypeptide, can be derivatised to the wells of the plate. Unbound target or protein can be trapped in the wells by antibody conjugation.

30 Methods for detecting such complexes, in addition to those described above for the GST-immobilized complexes, include immunodetection of complexes using antibodies which specifically bind to a „CVD gene“ polypeptide or test compound,

enzyme-linked assays which rely on detecting an activity of a „CVD gene“ polypeptide, and SDS gel electrophoresis under non-reducing conditions.

5 Screening for test compounds which bind to a „CVD gene“ polypeptide or polynucleotide also can be carried out in an intact cell. Any cell which comprises a „CVD gene“ polypeptide or polynucleotide can be used in a cell-based assay system. A „CVD gene“ polynucleotide can be naturally occurring in the cell or can be introduced using techniques such as those described above. Binding of the test compound to a „CVD gene“ polypeptide or polynucleotide is determined as
10 described above.

Modulation of Gene Expression

15 In another embodiment, test compounds which increase or decrease „CVD gene“ expression are identified. A „CVD gene“ polynucleotide is contacted with a test compound, and the expression of an RNA or polypeptide product of the „CVD gene“ polynucleotide is determined. The level of expression of appropriate mRNA or polypeptide in the presence of the test compound is compared to the level of expression of mRNA or polypeptide in the absence of the test compound. The test compound
20 can then be identified as a modulator of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater in the presence of the test compound than in its absence, the test compound is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less in the presence of the test compound than in its
25 absence, the test compound is identified as an inhibitor of the mRNA or polypeptide expression.

The level of „CVD gene“ mRNA or polypeptide expression in the cells can be determined by methods well known in the art for detecting mRNA or polypeptide.
30 Either qualitative or quantitative methods can be used. The presence of polypeptide products of a „CVD gene“ polynucleotide can be determined, for example, using a

variety of techniques known in the art, including immunochemical methods such as radioimmunoassay, Western blotting, and immunohistochemistry. Alternatively, polypeptide synthesis can be determined in vivo, in a cell culture, or in an in vitro translation system by detecting incorporation of labelled amino acids into a „CVD gene“ polypeptide.

Such screening can be carried out either in a cell-free assay system or in an intact cell. Any cell which expresses a „CVD gene“ polynucleotide can be used in a cell-based assay system. A „CVD gene“ polynucleotide can be naturally occurring in the cell or can be introduced using techniques such as those described above. Either a primary culture or an established cell line, such as CHO or human embryonic kidney 293 cells, can be used.

Therapeutic Indications and Methods

Therapies for treatment of CVD primarily relied upon effective drugs for lowering cholesterol and high blood pressure. In particular, the statins lower levels of arteriogenic lipoproteins and dramatically decrease clinical events and mortality from arteriosclerosis. Nevertheless, heart disease and stroke remain by far the most common causes of death in westernised societies, and new weapons, particularly agents that block disease at the level of the vessel wall or that raise anti-arteriogenic HDL, are needed. The advent of genomics-driven molecular target identification has opened up the possibility of identifying new cardiovascular disease-specific targets for therapeutic intervention that will provide safer, more effective treatments for CVD patients and arteriosclerosis patients in particular. Thus, newly discovered CVD-associated genes and their products can be tested for their role(s) in disease and used as tools to discover and develop innovative therapies. The identification of the ABC transporter presents exciting new opportunities for treatment of low HDL levels. Preliminary studies in animals suggest that it may be possible not only to block the development of arteriosclerosis but also to achieve significant regression. The most critical clinical aspect of arteriosclerosis is plaque rupture and thrombosis.

Genes playing important roles in any of the physiological processes outlined above can be characterized as cardiovascular disease targets. Genes or gene fragments identified through genomics can readily be expressed in one or more heterologous expression systems to produce functional recombinant proteins. These proteins are characterised in vitro for their biochemical properties and then used as tools in high-throughput molecular screening programs to identify chemical modulators of their biochemical activities. Modulators of target protein activity can be identified in this manner and subsequently tested in cellular and in vivo disease models for therapeutic activity. Optimisation of lead compounds with iterative testing in biological models and detailed pharmacokinetic and toxicological analyses form the basis for drug development and subsequent testing in humans.

The activities of the „CVD genes“ provide therapeutic targets for cardiovascular disease and arteriosclerosis in particular.

This invention further pertains to the use of novel agents identified by the screening assays described above. Accordingly, it is within the scope of this invention to use a test compound identified as described herein in an appropriate animal model. For example, an agent identified as described herein (e.g., a modulating agent, an antisense nucleic acid molecule, a specific antibody, ribozyme, or a human „CVD gene“ polypeptide binding molecule) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent. Furthermore, this invention pertains to uses of novel agents identified by the above described screening assays for treatments as described herein.

A reagent which affects human „CVD gene“ activity can be administered to a human cell, either in vitro or in vivo, to reduce or increase human „CVD gene“ activity. The reagent preferably binds to an expression product of a human „CVD gene“. If the

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expression product is a protein, the reagent is preferably an antibody. For treatment of human cells ex vivo, an antibody can be added to a preparation of stem cells which have been removed from the body. The cells can then be replaced in the same or another human body, with or without clonal propagation, as is known in the art.

5

In one embodiment, the reagent is delivered using a liposome. Preferably, the liposome is stable in the animal into which it has been administered for at least about 30 minutes, more preferably for at least about 1 hour, and even more preferably for at least about 24 hours. A liposome comprises a lipid composition that is capable of targeting a reagent, particularly a polynucleotide, to a particular site in an animal, such as a human. Preferably, the lipid composition of the liposome is capable of targeting to a specific organ of an animal, such as the lung, liver, spleen, heart brain, lymph nodes, and skin.

15 A liposome useful in the present invention comprises a lipid composition that is capable of fusing with the plasma membrane of the targeted cell to deliver its contents to the cell. Preferably, the transfection efficiency of a liposome is about 0.5 μg of DNA per 16 nmol of liposome delivered to about 10^6 cells, more preferably about 1.0 μg of DNA per 16 nmol of liposome delivered to about 10^6 cells, and even
20 more preferably about 2.0 μg of DNA per 16 nmol of liposome delivered to about 10^6 cells. Preferably, a liposome is between about 100 and 500 nm, more preferably between about 150 and 450 nm, and even more preferably between about 200 and 400 nm in diameter.

25 Suitable liposomes for use in the present invention include those liposomes usually used in, for example, gene delivery methods known to those of skill in the art. More preferred liposomes include liposomes having a polycationic lipid composition and/or liposomes having a cholesterol backbone conjugated to polyethylene glycol. Optionally, a liposome comprises a compound capable of targeting the liposome to a
30 particular cell type, such as a cell-specific ligand exposed on the outer surface of the liposome.

Complexing a liposome with a reagent such as an antisense oligonucleotide or ribozyme can be achieved using methods which are standard in the art (see, for example, U.S. Patent 5,705,151). Preferably, from about 0.1 μ g to about 10 μ g of polynucleotide is combined with about 8 nmol of liposomes, more preferably from about 0.5 μ g to about 5 μ g of polynucleotides are combined with about 8 nmol liposomes, and even more preferably about 1.0 μ g of polynucleotides is combined with about 8 nmol liposomes.

In another embodiment, antibodies can be delivered to specific tissues in vivo using receptor-mediated targeted delivery. Receptor-mediated DNA delivery techniques are taught in, for example, Findeis et al., (100); Chiou et al., (101); Wu & Wu, (102); Wu et al., (103); Zenke et al., (104); Wu et al., (105).

Determination of a Therapeutically Effective Dose

The determination of a therapeutically effective dose is well within the capability of those skilled in the art. A therapeutically effective dose refers to that amount of active ingredient which increases or decreases human „CVD gene“ activity relative to the human „CVD gene“ activity which occurs in the absence of the therapeutically effective dose.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays or in animal models, usually mice, rabbits, dogs, or pigs. The animal model also can be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

Therapeutic efficacy and toxicity, e.g., ED₅₀ (the dose therapeutically effective in 50% of the population) and LD₅₀ (the dose lethal to 50% of the population), can be determined by standard pharmaceutical procedures in cell cultures or experimental

animals. The dose ratio of toxic to therapeutic effects is the therapeutic index, and it can be expressed as the ratio, LD_{50}/ED_{50} .

Pharmaceutical compositions which exhibit large therapeutic indices are preferred.

5 The data obtained from cell culture assays and animal studies is used in formulating a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that include the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, sensitivity of the patient, and the route of administration.

10

The exact dosage will be determined by the practitioner, in light of factors related to the subject that requires treatment. Dosage and administration are adjusted to provide sufficient levels of the active ingredient or to maintain the desired effect. Factors which can be taken into account include the severity of the disease state, general health of the subject, age, weight, and gender of the subject, diet, time and frequency of administration, drug combination(s), reaction sensitivities, and tolerance/response to therapy. Long-acting pharmaceutical compositions can be administered every 3 to 4 days, every week, or once every two weeks depending on the half-life and clearance rate of the particular formulation.

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Normal dosage amounts can vary from 0.1 to 100,000 micrograms, up to a total dose of about 1 g, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

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If the reagent is a single-chain antibody, polynucleotides encoding the antibody can be constructed and introduced into a cell either ex vivo or in vivo using well-established techniques including, but not limited to, transferrin-polycation-mediated

DNA transfer, transfection with naked or encapsulated nucleic acids, liposome-mediated cellular fusion, intracellular transportation of DNA-coated latex beads, protoplast fusion, viral infection, electroporation, a gene gun, and DEAE- or calcium phosphate-mediated transfection.

5

Effective in vivo dosages of an antibody are in the range of about 5 µg to about 50 µg/kg, about 50 µg to about 5 mg/kg, about 100 µg to about 500 µg/kg of patient body weight, and about 200 to about 250 µg/kg of patient body weight. For administration of polynucleotides encoding single-chain antibodies, effective in vivo dosages are in the range of about 100 ng to about 200 ng, 500 ng to about 50 mg, about 1 µg to about 2 mg, about 5 µg to about 500 µg, and about 20 µg to about 100 µg of DNA.

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If the expression product is mRNA, the reagent is preferably an antisense oligonucleotide or a ribozyme. Polynucleotides which express antisense oligonucleotides or ribozymes can be introduced into cells by a variety of methods, as described above.

15

Preferably, a reagent reduces expression of a „CVD gene“ gene or the activity of a „CVD gene“ polypeptide by at least about 10, preferably about 50, more preferably about 75, 90, or 100% relative to the absence of the reagent. The effectiveness of the mechanism chosen to decrease the level of expression of a „CVD gene“ gene or the activity of a „CVD gene“ polypeptide can be assessed using methods well known in the art, such as hybridization of nucleotide probes to „CVD gene“ -specific mRNA, quantitative RT-PCR, immunologic detection of a „CVD gene“ polypeptide, or measurement of „CVD gene“ activity.

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In any of the embodiments described above, any of the pharmaceutical compositions of the invention can be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy can be made by one of ordinary skill in the art, according to conventional pharmaceutical

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principles. The combination of therapeutic agents can act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

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Any of the therapeutic methods described above can be applied to any subject in need of such therapy, including, for example, birds and mammals such as dogs, cats, cows, pigs, sheep, goats, horses, rabbits, monkeys, and most preferably, humans.

10

All patents and patent applications cited in this disclosure are expressly incorporated herein by reference. The above disclosure generally describes the present invention. A more complete understanding can be obtained by reference to the following specific examples which are provided for purposes of illustration only and are not intended to limit the scope of the invention.

15

Pharmaceutical Compositions

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The invention also provides pharmaceutical compositions which can be administered to a patient to achieve a therapeutic effect. Pharmaceutical compositions of the invention can comprise, for example, a „CVD gene“ polypeptide, „CVD gene“ polynucleotide, ribozymes or antisense oligonucleotides, antibodies which specifically bind to a „CVD gene“ polypeptide, or mimetics, agonists, antagonists, or inhibitors of a „CVD gene“ polypeptide activity. The compositions can be administered alone or in combination with at least one other agent, such as stabilizing compound, which can be administered in any sterile, biocompatible pharmaceutical carrier, including, but not limited to, saline, buffered saline, dextrose, and water. The compositions can be administered to a patient alone, or in combination with other agents, drugs or hormones.

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In addition to the active ingredients, these pharmaceutical compositions can contain suitable pharmaceutically acceptable carriers comprising excipients and auxiliaries

which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Pharmaceutical compositions of the invention can be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intraarterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, parenteral, topical, sublingual, or rectal means. Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combination of active compounds with solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. suitable excipients are carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, or sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethylcellulose, or sodium carboxymethylcellulose; gums including arabic and tragacanth; and proteins such as gelatin and collagen. If desired, disintegrating or solubilizing agents can be added, such as the cross-linked polyvinyl pyrrolidone, agar, alginic acid, or a salt thereof, such as sodium alginate.

Dragee cores can be used in conjunction with suitable coatings, such as concentrated sugar solutions, which also can contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments can be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as

glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with a filler or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds can be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration can be formulated in aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions can contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds can be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Non-lipid polycationic amino polymers also can be used for delivery. Optionally, the suspension also can contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions. For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention can be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes. The pharmaceutical composition can be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, succinic, etc. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preferred preparation can be a lyophilized powder which can contain any or all of the following: 150 mM histidine, 0.1%2% sucrose, and 27% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

Further details on techniques for formulation and administration can be found in the latest edition of REMINGTON'S PHARMACEUTICAL SCIENCES (106). After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. Such labeling would include amount, frequency, and method of administration.

Material and Methods

One strategy for identifying genes that are involved in cardiovascular disease is to detect genes that are expressed differentially under conditions associated with the disease versus non-disease conditions. The sub-sections below describe a number of experimental systems which may be used to detect such differentially expressed genes. In general, these experimental systems include at least one experimental condition in which subjects or samples are treated in a manner associated with cardiovascular disease, in addition to at least one experimental control condition lacking such disease associated treatment. Differentially expressed genes are detected, as described below, by comparing the pattern of gene expression between the experimental and control conditions.

Once a particular gene has been identified through the use of one such experiment, its expression pattern may be further characterized by studying its expression in a different experiment and the findings may be validated by an independent technique. Such use of multiple experiments may be useful in distinguishing the roles and relative importance of particular genes in cardiovascular disease. A combined approach, comparing gene expression pattern in cells derived from CVD patients to those of *in vitro* cell culture models can give substantial hints on the pathways involved in development and/or progression of CVD.

Among the experiments which may be utilized for the identification of differentially expressed genes involved in arteriosclerosis, for example, are experiments designed

to analyze those genes which are involved in foam cell formation. Such experiments may serve to identify genes involved in the differentiation of this cell type, or their uptake of enzymatic modified LDL.

5 Within such an experiment, human blood is drawn and peripheral monocytes are isolated by methods routinely practiced in the art. These human monocytes can then be used immediately or cultured *in vitro*, using methods routinely practiced in the art, for 4 to 6 days where they develop more macrophage-like characteristics such as the up-regulation of scavenger receptors. These cells are then treated for various lengths
10 of time with agents thought to be involved in foam cell formation. These agents include but are not limited to enzymatic modified LDL and HDL. Control monocytes that are untreated or directly treated with native HDL are grown in parallel. At a certain time after addition of the test agents, the cells are harvested and analyzed for differential expression as described in detail below in the following section.

15 In order to identify differentially expressed genes, RNA, either total or mRNA, were isolated from one or more blood samples of the subjects utilized in experiments such as those described earlier. Total RNA samples were obtained from peripheral white blood cells (PWBC) of experimental subjects and from corresponding PWBC of
20 control subjects.

Below are methods described for the identification of genes which are involved in cardiovascular disease, including but not limited to arteriosclerosis, ischemia/reperfusion, hypertension, restenosis, and arterial inflammation. Such genes represent
25 genes which are differentially expressed in cardiovascular disease conditions relative to their expression in normal, or non-cardiovascular disease conditions or upon experimental manipulation based on clinical observations. Such differentially expressed genes represent "target" and/or "marker" genes. Methods for the further characterization of such differentially expressed genes, and for their identification as
30 target and/or marker genes, are presented below.

Thus, a differentially expressed gene may have its expression activated or completely inactivated in normal versus cardiovascular disease conditions (e.g., treated with enzymatic modified LDL versus untreated; mimicking of cholesterol efflux due to HDL treatment), or under control versus experimental conditions. Such a
5 qualitatively regulated gene will exhibit an expression pattern within a given tissue or cell type which is detectable in either control or cardiovascular disease subjects, but is not detectable in both.

Alternatively, a differentially expressed gene may have its expression modulated, i.e.,
10 quantitatively increased or decreased, in normal versus cardiovascular disease states, or under control versus experimental conditions. The degree to which expression differs in normal versus cardiovascular disease or control versus experimental states need only be large enough to be visualised via standard characterisation techniques, such as, for example, the differential display technique described below. Other such
15 standard characterisation techniques by which expression differences may be visualised include but are not limited to quantitative RT-PCR and Northern analyses, which are well known to those of skill in the art.

Physiological and biochemical significance of the results:

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The Tables 1 and 2 show a summary of the genes, identified by the differential expression approach with DNA array technology and TaqMan analysis, which show an excellent correlation of gene expression levels.

25 All 74 nucleotide sequences were previously described in the literature but have not been previously recognised as being differentially expressed in CVD patients versus non-CVD patients.

30 Of these 74 nucleotide sequences, several are coding for transporter or channel proteins (e.g., voltage dependent anion channel1 (VDAC1), calmodulin like). These transporters can play an important role in the import and export of cholesterol or

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triglycerides, one of the key steps in the generation of lipid vessels in macrophages, and if dysregulated, one step in direction of arteriosclerosis. The VDAC protein is thought to form the major pathway for movement of adenine nucleotides through the outer membrane and to be the mitochondrial binding site for hexokinase and glycerol kinase. And may also be involved in the signalling and initiation of an apoptotic cascade in the cell involving the BCL2 protein. The BCL2 family of proteins (see Bfl1), whose members may be anti-apoptotic or pro-apoptotic, regulates cell death by controlling this mitochondrial membrane permeability during apoptosis. Since macrophages transformed by high LDL load into foam cell are driven into apoptosis, within the so called fatty streaks, the upregulation of these genes can function as an indicative marker for arteriosclerosis. Some of the genes identified, belong to a signalling pathway system (e.g., epimorphin, lipoxin or G-CSFR). All represent receptors, mediating cell to cell interactions. Also isomerases and oxidoreductases show a tightly regulated expression pattern upon incubation with eLDL (e.g., IPP isomerase, 5-lipoxygenase, further see Table 4). These enzymes are involved in the degradation of fatty acids or in the synthesis of cholesterol. Some of the genes listed in the Tables 1 and 2 are involved in the phagosomal degradation of fatty acids (e.g., legumain or cathepsin L), which reflects the predispositional changes in the CVD patients analyzed. These genes were not directly affected by a mutation (in case of Tangier's Disease; ABCA1 transporter) but were differentially regulated upon comparison with the same gene in normal individual under the same eLDL conditions. So one can assume that these genes are good candidates for a diagnostic test or therapeutic interaction.

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EXAMPLE 1Probe selection for the differential gene expression analysisProband and Patient Selection

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For Expression analysis monocytes from healthy donors with Apo E3/E3 and E4/E4 genotype, as well as from Tangier's disease, familial hypercholestermia, Niemann Pick Type C and Lp(a) patients were isolated as described below. Probands and patients were identified and selected due to their clinical appearance and further
10 genetic confirmation of the represented genotypes. For each group two individual were selected and expression profiles generated as described below. In total we have analysed RNA from 9 male and 9 female donors.

Monocyte Isolation and Cultivation

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Human peripheral blood leukocytes from healthy normolipidemic volunteers were isolated by leukapheresis in a cell separator and subsequent counterflow centrifugation as described by Mueller et al; (107). To guarantee viability of the cells with minimal activation, isolated monocytes were cultured on Ultra Low Attachment
20 Surfaces (Costar) in macrophage serum-free medium (Life Technologies) supplemented with monocyte colony-stimulating factor (M-CSF, 50 ng/ml) for up to 6 days. Cells were detached by rinsing the Costar Ultra Low Attachment Surfaces with PBS. For uptake experiments, 4-day cultured monocytes (10^6 cells per milliliter) were incubated with modified LDL for 2 hours at 37°C in 1 ml macrophage media
25 containing 0.5% BSA.

Preparation of LDL

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Human native LDL (1.006 mg/mL, density, 1.063 mg/ml) was isolated from the plasma of healthy blood donors by sequential preparative ultracentrifugation in KBr

gradients, followed by extensive dialysis and filter sterilization. Protein concentrations were determined by use of Lowry's method.

Chemical and Enzymatic Modification of LDL

5 Enzyme treatment was conducted with trypsin (6.6 mg/ml, Sigma) and cholesterol esterase (40 mg/ml, Roche Biochemica) for 6 to 8 hours at 37°C. Subsequently, the pH of the solution was adjusted to 5.5 by addition of MES buffer, pH 5.0. Finally, neuraminidase (79 mU/ml, Behring) and magnesium ascorbate solution (30 mg/ml)
10 were added for 14 hours at 37°C. The absence of oxidation products in E-LDL was verified by the determination of thiobarbituric acid-reactive substances to quantify lipid peroxidation products.12 Modified lipoproteins were stored at 4°C and used within a week. During LDL preparation and subsequent modification, general precautions were taken to avoid LPS contamination. The latter was excluded by
15 *Limulus* endotoxin assay (Kinetic-QCL, BioWhittaker).

EXAMPLE 2

Differential DNA expression profiling

20 Expression profiling was carried out using the Affymetrix Array Technology. With minor modifications, the sample preparation protocol followed the Affymetrix GeneChip Expression Analysis Manual (Santa Clara, CA). Total RNA extraction and isolation from PWBC can be performed by using TRIzol (Life Technologies, Rockville, MD) and Oligotex mRNA Midi kit (Qiagen, Hilden, Germany), and an
25 ethanol precipitation step should be carried out to bring the concentration to 1 mg/ml. Using 5–10 mg of mRNA to create double stranded cDNA by the SuperScript system (Life Technologies). First strand cDNA synthesis was primed with a T7-(dT24) oligonucleotide. The cDNA can be extracted with phenol/chloroform and precipitated with ethanol to a final concentration of 1 mg /ml. From the generated cDNA,
30 cRNA can be synthesised using Enzo's (Enzo Diagnostics Inc., Farmingdale, NY) *in vitro* Transcription Kit. Within the same step the cRNA can be labelled with biotin

nucleotides Bio-11-CTP and Bio-16-UTP (Enzo Diagnostics Inc., Farmingdale, NY). After labelling and cleanup (Qiagen, Hilden (Germany)) the cRNA then should be fragmented in an appropriated fragmentation buffer (e.g., 40 mM Tris-Acetate, pH 8.1, 100 mM KOAc, 30 mM MgOAc, for 35 minutes at 94 °C). As per the Affymetrix protocol, fragmented cRNA should be hybridised on the HG_U95 array set (five chips A-E), comprising app. 13.000 probed transcripts each, for 24 hours at 60 rpm in a 45 °C hybridization oven. After Hybridization step the chip surfaces have to be washed and stained with streptavidin phycoerythrin (SAPE; Molecular Probes, Eugene, OR) in Affymetrix fluidics stations. To amplify staining, a second labeling step can be introduced, which is recommended but not compulsive. Here one should add SAPE solution twice with an antistreptavidin biotinylated antibody.

Hybridization to the probe arrays may be detected by fluorometric scanning (Hewlett Packard Gene Array Scanner; Hewlett Packard Corporation, Palo Alto, CA). After hybridization and scanning, the microarray images can be analyzed for quality control, looking for major chip defects or abnormalities in hybridization signal. Therefor either Affymetrix GeneChip MAS 4.0 Software or other microarray image analysis software can be utilized. Primary data analysis should be carried out by MAS Software.

In case of the genes analyses in one embodiment of this invention the primary data have been analysed by further bioinformatic tools and additional filter criteria. The bioinformatic analysis is described in detail below.

74 genes were identified to be at least 1.5 fold, differentially expressed in patients with cardiovascular disease in comparison to patients without cardiovascular disease. Due to the diversity of the group of cardiovascular disease patients, an inter group comparison was performed, to identify those genes and pathways that are involved in either differentiation and/or expressional reaction of macrophages under lipid stress (high eLDL environment). The differential expression of these 74 genes may only be observed in one group, (e.g. Tangier disease patients), due to the inherited mutation

in a specific gene in these patients and the resulting abnormal lipid trafficking. The specific regulation of these genes within one group compared to the others indicates their role in lipid trafficking and development of arteriosclerosis.

5 To confirm the results obtained by the array analysis with a second independent experimental approach, these 74 genes were analyzed by real-time quantitative PCR (TaqMan), using the PRISM 7700 Sequence Detection System of PE Applied Biosystems (Perkin Elmer, Foster City, CA, USA) with in the same cohort. Within
10 this technique a fluorogenic probe, consisting of an oligonucleotide labelled with both a fluorescent reporter dye and a quencher dye, is included in a typical PCR. Amplification of the probe-specific product causes cleavage of the probe, generating an increase in reporter fluorescence. Primers and probes were selected using the Primer Express software and localized mostly in the 3' region of the coding sequence or in the 3' untranslated region (see Table 3 for primer- and probe- sequences)
15 according to the positions of the probe sequence used for the construction of the Affymetrix HG_U95A-E chip. All primer pairs were checked for specificity by conventional PCR reactions. To standardise the amount of sample RNA, GAPDH was selected as a reference, since it was not differentially regulated in the samples analyzed. TaqMan validation experiments were performed showing that the
20 efficiencies of the target and the control amplifications are approximately equal which is a prerequisite for the relative quantitation of gene expression by the comparative $\Delta\Delta C_T$ method, known to those with skills in the art.

EXAMPLE 3

25

Data analysis

According to Affymetrix measurement technique (Affymetrix GeneChip Expression Analysis Manual, Santa Clara, CA) a single gene expression measurement on one
30 chip yields the average difference value and the absolute call. Each chip contains 16–20 oligonucleotide probe pairs per gene or cDNA clone. These probe pairs include

perfectly matched sets and mismatched sets, both of which are necessary for the calculation of the average difference, or expression value, a measure of the intensity difference for each probe pair, calculated by subtracting the intensity of the mismatch from the intensity of the perfect match. This takes into consideration variability in hybridization among probe pairs and other hybridization artefacts that could affect the fluorescence intensities. The average difference is a numeric value supposed to represent the expression value of that gene. The absolute call can take the values 'A' (absent), 'M' (marginal), or 'P' (present) and denotes the quality of a single hybridization. We used both the quantitative information given by the average difference and the qualitative information given by the absolute call to identify the genes which are differentially expressed in biological samples from individuals with cardiovascular disease versus biological samples from the normal population. With other algorithms than the Affymetrix one we have obtained different numerical values representing the same expression values and expression differences upon comparison.

The differential expression E in one of the cardiovascular disease groups compared to the normal population is calculated as follows. Given n average difference values d_1, d_2, \dots, d_n in the cardiovascular disease population and m average difference values c_1, c_2, \dots, c_m in the population of normal individuals, it is computed by the equation:

$$E \equiv \exp\left(\frac{1}{m} \sum_{i=1}^m \ln(c_i) - \frac{1}{n} \sum_{i=1}^n \ln(d_i)\right)$$

If $d_j < 50$ or $c_i < 50$ for one or more values of i and j , these particular values c_i and/or d_j are set to an "artificial" expression value of 50. These particular computation of E allows for a correct comparison to TaqMan results.

A gene is called up-regulated in cardiovascular disease versus normal if $E \geq 1.5$ and if the number of absolute calls equal to 'P' in the cardiovascular disease population is greater than $n/2$.

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A gene is called down-regulated in cardiovascular disease versus normal if $E \leq 1.5$ and if the number of absolute calls equal to 'P' in the normal population is greater than $m/2$.

- 5 The final list of differentially regulated genes consists of all up-regulated and all down-regulated genes in biological samples from individuals with cardiovascular disease versus biological samples from the normal population. Those genes on this list which are interesting for a pharmaceutical application were finally validated by TaqMan. If a good correlation between the expression values/behavior of a transcript
- 10 could be observed with both techniques, such a gene is listed in Table 1 or 2.

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TABLE 1

Genes which are up-regulated in diseased vs. Normal individuals

DNA Sequence	Protein Sequence	GB Acc	UNIGENE	LocustLink	Gene Name	Short Description of the Gene	Minimal Fold Change
SEQ ID NO. 37	SEQ ID NO.111	L32976	Hs.89449	4296	MLK-3 MLK3	HUMMLK3A protein kinase (MLK-3) mRNA, complete cds	7,0
SEQ ID NO. 6	SEQ ID NO.80	X13988	Hs.17384	4621	MYH3	mRNA for embryonic myosin heavy chain	5,0
SEQ ID NO. 70	SEQ ID NO.144	M98479	Hs.8265	7052	TGM2	tissue transglutaminase	5,0
SEQ ID NO. 60	Seq_ID134	U82812	Hs.522	922	CD5L	scavenger receptor cysteine rich Sp alpha mRNA, complete cds	4,0
SEQ ID NO. 72	SEQ ID NO.146	X03663	Hs.174142	1436	CSF1R	c-fms	4,0
SEQ ID NO. 65	SEQ ID NO.139	AF001383	Hs.193163	274	SH3P9 AMPHL	amphiphysin II mRNA, complete cds	3,5
SEQ ID NO. 9	SEQ ID NO.83	AB001325	Hs.234642	360	AQP3	AQP3 gene for aquaporin 3 (water channel), partial cds	3,0
SEQ ID NO. 11	SEQ ID NO.85	U61538	Hs.8531	11261	CHP	calcium-binding protein chp mRNA, complete cds	3,0
SEQ ID NO. 19	SEQ ID NO.93	Y08374	Hs.75184	1116	HTG; HTGS_PHAS	gene encoding cartilage GP-39 protein, exon 1 and 2 (and joined CDS)	3,0
SEQ ID NO. 33	SEQ ID NO.107	D17793	Hs.78183	8644	ets variant gene 6	mRNA for KIAA0119 gene, complete cds	3,0
SEQ ID NO. 42	SEQ ID NO.116	D14582	Hs.99865	2054	STX2C STX2B STX2A EPIM	mRNA for epimorphin	3,0
SEQ ID NO. 46	SEQ ID NO.120	AJ000414	Hs.73999	9322	TRIP10	mRNA for Cdc42-interacting protein 4 (CIP4)	3,0
SEQ ID NO. 48	SEQ ID NO.122	U48734	Hs.182485	81	ACTN4	non-muscle alpha-actinin mRNA,	3,0

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DNA Sequence	Protein Sequence	GB Acc	UNIGENE	LocustLink	Gene Name	Short Description of the Gene	Minimal Fold Change
SEQ ID NO. 63	SEQ ID NO.137	H24861	Hs.117167			y142e11.r1 cDNA, 5 end	3,0
SEQ ID NO.74	SEQ ID NO.148	AF057557	Hs.58831	9214	TOSO	anti-Fas-induced apoptosis mRNA	3,0
SEQ ID NO. 13	SEQ ID NO.87	U22662	Hs.81336	10062	LXRA LXR-A	nuclear orphan receptor LXR-alpha mRNA, complete	2,5
SEQ ID NO. 55	SEQ ID NO.129	L26232	Hs.2837	5360	PLTP	phospholipid transfer protein mRNA, complete cds	2,5
SEQ ID NO. 7	SEQ ID NO.81	AB026833	Hs.241551	9635	CLCA2	mRNA for chloride channel protein, complete cds	2,0
SEQ ID NO. 17	SEQ ID NO.91	J04430	Hs.1211	54	ACP5	HUMACP5 tartrate-resistant acid phosphatase type 5	2,0
SEQ ID NO. 24	SEQ ID NO.98	X17025	Hs.7638	3422	IDI1	log of yeast IPP isomerase	2,0
SEQ ID NO. 26	SEQ ID NO.100	J03600	Hs.89499	240	LOX5 ALOX5	HUMLOX5 lipoxygenase mRNA, complete cds	2,0
SEQ ID NO. 35	SEQ ID NO.109	AF004709	Hs.178695	5603	SAPK4 PRKM13	stress-activated protein kinase 4 mRNA,	2,0
SEQ ID NO. 43	SEQ ID NO.117	M59818	Hs.2175	1441	G-CSFR-1 CSF3R	granulocyte colony-stimulating factor receptor (G-CSFR-1) mRNA, complete cds	2,0
SEQ ID NO. 59	SEQ ID NO.133	AL034562	Hs.156114	8194	1199_at PTPNS1	dJ684O24.2 (prodynorphin (Beta-Neoeendorphin-Dynorphin precursor, Proenkephalin B	2,0
SEQ ID NO. 64	SEQ ID NO.138	AF089750	Hs.179986	10211	FLOT1	flotillin-1 mRNA, complete cds	2,0
SEQ ID NO. 45	SEQ ID NO.119	AB006780	Hs.621	3958	GALBP MAC2	mRNA for galectin-3, complete cds	1,8
SEQ ID NO. 53	SEQ ID NO.127	U30930	Hs.15854	7368	UGT8	UDP-Galactose ceramide galactosyl transferase (CGT) mRNA	1,8

TABLE 2

Genes which are down-regulated in diseased vs. Normal individuals

DNA Sequence	Protein Sequence	CB_Ace	UNIGENE	LocusLink	Gene Name	Short Description of the gene	Minimal Fold Change
SEQ ID NO. 50	SEQ ID NO. 124	U03644	Hs.89421	9541		receptin mRNA, complete cds	- 6,0
SEQ ID NO. 61	SEQ ID NO. 135	X82460	Hs.77348	3248	HPGD	hydroxyprostaglandin dehydrogenase 15-(NAD)	- 6,0
SEQ ID NO. 31	SEQ ID NO. 105	Y13647	Hs.119597	6319	SCD	mRNA for stearoyl-CoA desaturase	- 5,0
SEQ ID NO. 56	SEQ ID NO. 130	U41387	Hs.169531	9188		Gu protein mRNA, partial cds	- 5,0
SEQ ID NO. 66	SEQ ID NO. 140	U69274	Hs.2861	27107		zinc finger protein mRNA, complete cds	- 5,0
SEQ ID NO. 73	SEQ ID NO. 147	S70154	Hs.278544	39	ACAT2	cytosolic acetoacetyl-coenzyme A thiolase, CT	- 5,0
SEQ ID NO. 28	SEQ ID NO. 102	U78294	Hs.111256		ALOX15B	15S-lipoxygenase mRNA, complete cds	- 4,0
SEQ ID NO. 44	SEQ ID NO. 118	U40572	Hs.172278	6645	SNT2B2	beta2-syntrophin (SNT B2) mRNA, complete cds	- 4,0
SEQ ID NO. 47	SEQ ID NO. 121	Z11793	Hs.3314	6414	SEPP1	mRNA for selenoprotein P	- 3,5
SEQ ID NO. 4	SEQ ID NO. 78	AF046873	Hs.125878	8224	SYN3	synapsin IIIa mRNA, complete cds	- 3,0
SEQ ID NO. 22	SEQ ID NO. 96	U27467	Hs.227817	597	Bfl-1 U2746 BCL2A1	HSU27467 Bcl-2 related (Bfl-1) mRNA, complete cds	- 3,0
SEQ ID NO. 25	SEQ ID NO. 99	AF061741	Hs.17144	9249	SDR1	retinal short-chain dehydrogenase reductase retSDR1 mRNA, complete cds	- 3,0
SEQ ID NO. 27	SEQ ID NO. 101	AB016247	Hs.28831	6309	C5D SC5DL	mRNA for sterol-C5-desaturase, complete cds	- 3,0

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DNA Sequence	Protein Sequence	GB Acc	UNIGENE	Locustlink	Gene Name	Short Description of the gene	Minimal Fold Change
SEQ ID NO. 49	SEQ ID NO.123	X68733	Hs.234726	12	ACT AACT	gene for alpha1-antichymotrypsin, exon 1	- 3,0
SEQ ID NO. 51	SEQ ID NO.125	Y09443	Hs.2258	8540	AGPS	mRNA for alkyl-dihydroxyacetonephosphate synthase precursor	- 3,0
SEQ ID NO. 58	SEQ ID NO.132	AB000220	Hs.171921	10512	IFN-alpha 6 SEMA3C	AB000220 mRNA for semaphorin E, complete cds	- 3,0
SEQ ID NO. 2	SEQ ID NO.76	U69108	Hs.29736	7188	U6910 TRAF5	HSU69108 TNF receptor associated factor 5 mRNA, partial cds	- 2,5
SEQ ID NO. 3	SEQ ID NO.77	L02320	Hs.25613	5962	RDX	radixin mRNA, complete cds	- 2,5
SEQ ID NO. 12	SEQ ID NO.86	AF026166	Hs.6456	10576	RBP-MS/type 4 CCT2	chaperonin-containing TCP-1 beta subunit log mRNA, complete cds	- 2,5
SEQ ID NO. 14	SEQ ID NO.88	U22431	Hs.19754	3091	HIF-1 alpha U2243 HIF1A	HSU22431 hypoxia-inducible factor 1 alpha (HIF-1 alpha) mRNA, complete cds	- 2,5
SEQ ID NO. 18	SEQ ID NO.92	AB020645	Hs.239189	2744	KIAA0838 Hs.172839	mRNA for KIAA0838 protein, complete cds	- 2,5
SEQ ID NO. 34	Seq ID108	Y12735	Hs.3818	8444	DYRK3	mRNA for protein kinase, Dyk3	- 2,5
SEQ ID NO. 36	SEQ ID NO.110	X60188	Hs.861	5595	ERK1 ERK1 PRKM3	HSEK1 ERK1 mRNA for protein serine threonine kinase	- 2,5
SEQ ID NO. 54	SEQ ID NO.128	Z35102	Hs.8724	11329	protein kinase C inhibitor NDR	HSERKINX mRNA for Ndr protein kinase	- 2,5
SEQ ID NO. 69	SEQ ID NO.143	M80482	Hs.17414	5046	PACE4	subtilisin-like protein (PACE4)	- 2,5
SEQ ID NO. 5	SEQ ID NO.79	M59830	Hs.27442	3304		MHC class III HSP70-2 gene (HLA), complete cds	- 2,2
SEQ ID NO. 1	SEQ ID NO.75	X58965	Hs.275163	4831	nm23-H2	RNA for nm23-H2 gene	- 2,0

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DNA Sequence	Protein Sequence	GB Acc	UNIGENE	LocusLink	Gene Name	Short Description of the gene	Minimal Fold Change
SEQ ID NO. 8	SEQ ID NO.82	AB008775	Hs.14624	366	AQP9	AQP9 mRNA for aquaporin 9, complete cds	- 2,0
SEQ ID NO. 15	SEQ ID NO.89	U51903	Hs.78993	10788	IQGAP2	HSU51903 RasGAP-related protein (IQGAP2) mRNA, complete cds	- 2,0
SEQ ID NO. 16	SEQ ID NO.90	AF056490	Hs.78746	5151	rac protein kinase-alpha PDE8A	cAMP-specific phosphodiesterase 8A (PDE8A) mRNA, partial cds	- 2,0
SEQ ID NO. 20	SEQ ID NO.94	D55696	Hs.1869	5641	PRSC1	mRNA for cysteine protease, complete cds	- 2,0
SEQ ID NO. 21	SEQ ID NO.95	X12451	Hs.7856	1514	CTSL	mRNA for pro-cathepsin L (major excreted protein MEP)	- 2,0
SEQ ID NO. 23	SEQ ID NO.97	S81221	Hs.93199	4047	LSS	lanosterol synthase [, fetal liver, mRNA Partial, 2637 nt]	- 2,0
SEQ ID NO. 29	SEQ ID NO.103	AL050118	Hs.184641	9415	DKFZp586C201	mRNA; cDNA DKFZp586C201 (from clone DKFZp586C201)	- 2,0
SEQ ID NO. 30	SEQ ID NO.104	AF034544	Hs.1186	1717	DHCR7	delta7-sterol reductase mRNA, complete cds	- 2,0
SEQ ID NO. 32	SEQ ID NO.106	X77094	Hs.196352	4689	NCF4	mRNA for p40phox	- 2,0
SEQ ID NO. 38	SEQ ID NO.112	X13916	Hs.89137	4035	LRP1	mRNA for LDL-receptor related protein	- 2,0
SEQ ID NO. 39	SEQ ID NO.113	W60864	Hs.9963	7305	TYROBP	zd27g05.s1 cDNA, 3 end	- 2,0
SEQ ID NO. 40	SEQ ID NO.114	X74039	Hs.179657	5329	PLAUR	mRNA for urokinase plasminogen activator receptor	- 2,0
SEQ ID NO. 57	SEQ ID NO.131	Y08136	Hs.42945	10924	ASM3A ASML3a	mRNA for ASM-like phosphodiesterase 3a	- 2,0
SEQ ID NO. 67	SEQ ID NO.141	U49392	Hs.76364	199	AIF1	allograft inflammatory factor-1 (AIF-1) mRNA, complete cds	- 2,0
SEQ ID NO. 68	-----	AF035284	Hs.12214	3992		clone 23716 mRNA sequence	- 2,0
SEQ ID NO. 41	SEQ ID NO.115	M84562	Hs.99855	2358	FPRL1	formyl peptide receptor-like receptor (FPRL1)	- 1,8

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DNA Sequence	Protein Sequence	CB_Acc	UNIGENE	LocusLink	Gene Name	Short Description of the gene	Minimal Fold Change
SEQ ID NO. 52	SEQ ID NO.126	M58597	Hs.2173	2526	FUT4	mRNA, complete cds ELAM-1 ligand fucosyltransferase (ELFT) mRNA, complete cds	- 1,8
SEQ ID NO. 62	SEQ ID NO.136	S60099	Hs.64797	334	APPH	APPH amyloid precursor protein log [, placenta, mRNA, 3727 nt]	- 1,8
SEQ ID NO. 71	SEQ ID NO.145	D38048	Hs.11865	5695	PSMB/	proteasomal subunit Z	- 1,8
SEQ ID NO. 10	SEQ ID NO.84	L06132	Hs.149155	7416	VDAC1	voltage-dependent anion channel isoform 1 (VDAC) mRNA, complete cds	- 1,6

TABLE 3

Gene	5' primer	3' primer
L26232	CTGCGCAGGTTCCGAATCT	GGGCTGTAATGGGATCAGA
AF061741	ACAGCACCTGGGCACACAC	GTCCTGCTCACCCAGCAGA
U41387	TCCTTCCCTGAAATAAATACCTAAGG	GCAGGTGGCTGAGGAAACC
L00352	TCTGGATCGTTTGACGGGA	TCTCTCCGGACATCAGTGCA
AF056490	CGCCTAATGCACCTTCACAGGT	AAATAGAGTAGACTTTTGGAAATTGAAATTATAAA
U22662	TCTGTTTTCTTGGCCGGATG	TGCCCTTCTCAGTCTGTTCCTCA
J036600	AAACACCATAGGGACCCATTCTAC	GATTTGCTGTGCTGCTTGG
Y09443	ATCCTTGCTAATGGAGGGAGC	CCTTTAGCCATTGCTTCCGTA
Y12735	GCTAACTTAATGTGAGAAACCAATGG	ATACACATATGCATCTCTGGGCA
Y08136	GAATCTAAAGGGAGAGTCCATCTGG	TCCGGCTGCAAAATCTTCAAT
AB026833	TTATTGACCTGGAAAGCTGTAAAAGTAGA	TAGCCTGGCCCTGATCAAAG
AF004709	TGTCGGTTGGGAGAAACTAGCT	CTGCAGGCGGATTCTCCAGAT
X74039	CCATGTGGAGATAGAGCCCC	GGCTACATGTCCAAGGTGGC
AB016247	TGATGTTTGAAAGTTACAACCTGTAATTTT	GGAGAAGAGGAGGAATAAGATTTTAGAA
U03644	AAGGGAGACAAAGGAAACGGG	CTCTATACAAAGTCTGTGCCATGGC
U78294	TCCAAGCCTCAAAGTGCCC	CCACGGCTGTAAACGCAAA
AB000220	GTAATCTCTGCACCGCTGCC	CATCCCAGGCGCAATAAGG
AB000220	AAAAGCACAAAGCGAACCCCC	CACAAACCCACGCTGCA

Gene	5' primer	3' primer
D17793	GCTGGAGGTGCTGGTAGCTG	TGTTGGTGCCCTGCCCTTC
AL050118	ATTGCCCTTTCAGCTCTAGATCCC	CAGTTCAACACCCGTGCACG
AF0374544	GGGCACTGCTGAGGAATGAT	CCGAACAACATCTGGCATTTT
AB016247	ACCAGCAAGGCTGACCTGTC	CTCAAATACATCAAGCACAGCCTTA
AF089747	CAGAAAGAGGAATAAAATGATTAAAGTGC	TCTCTGCCTCTGATTACAGGGTT
K02268	GACCCGGAAACACGCGTATCA	ATCCGACCTCTGACCCCTGG
AF019562	AGCAACACCTCCCTATTCTGTATTT	ACACGTCATGAAAGGTCTAGGATT
U82812	CCTGCCCTCCTGCCAAAG	GGGCTCAAAATGCTGTAGGTTGT
AL034562	GCCACGATCAACAATCTGCAG	AATTCCCAGCCCCACTCAG
J04430	GCCGCTGACTTCTTTCACAAG	CCTCCAAGGACAAATCCAGCA
M58597	CTCGGTGCTGGGAGGGT	GGTGTCCTTTGTCAAAGAGCATG
S81221	CCCTGACTAACAGCCTCAGCA	TTGGCCTCGTCTTCACTTGG
AF046873	GCCTTTAAGTGACTAAGGAACAACATAG	TTGAGAGGCACAAATTGAAGTATTCA
U51903	CTGACCCCTCGGCCTCTACTTT	TGGTGTGGTCTTCTCTGAGTGAA
S60099	GTCAAAAAGCCCAGAAATCCC	TTCACATTTAATTTCTGCTGTTCTGA
AB008775	CTATGGCCGAGGGTGAAGAC	GTAGGAGGTGGGCACGTAGC
AJ000414	CCCTAATGCCAGTTCCAGCTT	AGCCCCAAATCAGGGGACAC
M84562	CAGGATTTCCTACTGGACCTTG	ACCCAAATTCGGGTCCAC
AB001325	AAGAACGCCCTGGAGTCCTAC	TCGGCCTCGCTGATCTTG

CVID-gene	5' primer	3' primer
M59830	CATAGGAAAATGATCAACAAGCAA	GGATGAGCGTAAGGCAGTAAGAA
H24861	GACTTTTTTAGACAGATCTTCATGACCTG	ACCCTGCAGACCTTTTGGTG
L06132	AGCCTCATAGCTGAAGTTGCCT	TCAATGGACATGCTCAGGGA
AF089750	CACAGCACAAACCGGTCCC	CCCTCGCATGGCCCCA
U48734	AAACCCCAACCCTAGTTTCCCT	CGCGAAGTGACAGCTTTGAC
X60188	TTCACTGAGAGGGTCCCATGA	GAACCAACACATTTTTCGGGAG
AF001383	TCCCATGCTTGAGCTTCCA	CTACCTGTCTCCATGGCTTGC
AB020645	GCCATCTTGCCAGGATTAAA	AAGGAACCTGAGGGACCCC
Y13647	CTGTCTGCTTGGAGTTTACATATCAAA	AACCCAATTGGCCAGACAAAA
U69274	CTCTGTTCGGGAGCGGAG	AGCTCGTCGTCTGTGGTGGT
D14582	CTCAGCCGGGAAGATTCC	CATTGATGATCCGGTCCCC
U61538	TCATGCAGACCGGGTACAAC	GAAAGGTGGTAGCCGATGAG
Z35102	GATTTTGGTGGTCCCGAGG	TGCAACACAAATACAAATCGGC
U40572	GCTGAGCTGGAATTGCCA	CGCAAACCAACTGTTTTCACC
L02320	CCTGTGATCCTTTGATGGCTTT	CATCAGTAAACTCTCCTAGGGAGCTAC
AL137751	CAACTTGAGGAGAAAACCTTTACAATT	GGTGACAAATGAAACTCTGTCTCAGA
U69108	CTTCCCTCGGAAGCTGCAC	ACCGTCAGCTCATGGCATC
X77094	CATGCCCTTATGAGACTACTAATGAAATT	GGTTCAAGTGCCAAACTCTCTACA
U30930	TCCGGCGCTAAGACTCGAGAC	AATATACATTTTGCCATATCTTCTGTCTG

CvD-gene	5' primer	3' primer
X13988	ACCTGCCCTGCTCTGC	GCTAGCCCAGATACCTGTTTGAG
Y08374	CCACAACACACAGATTGAGCTC	GATGCCTCACTATCCCCACAG
M80927	GGGTCTATTGTCTCCGCTAAAA	GAAAGAAATGGAAGACGCTGAAC
AF077200	TCCCACTGTCAATCAAGACCTAA	GCTGGGTATCCTGTAAAGTAGCAATC
XM016472	CTCTCTGGATGCCCTTCCTGC	TTCTGGCTTCACTGGATCCC
L32976	CAGGACCTTCTTCACAAGATGACTT	CCCACCCTAATTGTAGTTTTTCAG
D55696	ACAGGCCGAGTGATGCTTG	CAGAAAGTCCCCACGAATGGT
X58965	GCGTGTGGACAACATCATCAA	GATCGACAGCACGTGGGAAT
AF026166	GAGGTCCATAAGCCCCATGAC	GCAGATCGCCTGGGAGG
M59818	TTTAATGAGAAATAGAAACGTAAACTATGACC	AAGTAATAATTGTTTGAGAGATAAGTAAAGGAAA
Z11793	AGGTGTCCAGTGGCTCCG	TTAGGATGGCAGATCTCTTGCC
U49392	GAATTGGAACATTATTACAGCAGCC	CACTAGATTTCATCCTTTTACACG
U22431	GACTATCTGCAGTGGCTCCTACAG	AACATTTTGTAGCACTCTGGACGTT
U27467	CCCTCCAAACCCACAGCC	AATATGCCTAGAGTAGATGCTGCTGAA
AF035284	TGTGCATTGCAGGATGGTG	TGGCAACATCCGGCATAAC
X17025	GACACTTTGCCAAGGCTCTCC	CATCCTTTCCCGCCTACCTC
X13916	CAAAGACCGGAGAAACCATTTG	ATCACCGTCCACCAGCTCA
X12451	TTGCAGAGGCGCTGCTG	TGTACACCTGCTTCAAGATTCCA
X82460	GCTCCCCCTGTTTGACGACA	TTAGGGTTAACATTGTACTTGCTTCATT

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CvD-gene	5' primer	3' primer
M80482	AGCTGGAGAGAAACCCAGATGTTGTTATTGAATC	GCTCCCCCTGTTTGACGACA
M55153	TTAGCAGGACTCATGCCCCG	ATCCAACCTATGCCATGCTTTGA
M98479	AAGGACTTGGAGAGAAATCATGCTGTTGCA	TCCAGGGCCCCCCA
X82460	TGCACAGCAGCCGGTTTATTGTGC	TTAGCAGGACTCATGCCCCG
D38048	GCCAGCCACCCACTGATGCCA	CCAAACAATGGACACCTTCCTGA
X03663	CCTCTGGGAGATCTTCTCACTTGGGCTG	AGAGCGACGTCTGGTCTCTATG
S70154	AATAGGACCAATTCCAGCCATAAAGCAAGCT	AGTGGGTGTGGAGCCCTTCC

TABLE 4

Gene Accession	Detailed Description	Enzyme Class	Biological Function	Subcellular
X58965		Metabolism		
U69108	Member of a family of proteins that interact with the cytoplasmic domain of oligomerized TNF receptors, binds the lymphotoxin beta receptor (LTBR)	activator of NF-kappa B		Cytoplasmic
L02320	Radixin, member of a family of proteins that link the cytoskeleton and the plasma membrane, thereby regulating cell adhesion and cortical morphogenesis	Anchor Protein Proteasome		Cytoskeletal
AF046873	Synapsin III, a synaptic vesicle protein, a member of a family of proteins that bind ATP and may regulate neurotransmitter release	ATPase	Hydrolase	Cytoplasmic
M59830	Member of the heat shock HSP70 family of molecular chaperones that are involved in protein folding, translocation, and assembly into complexes, inducible by heat shock	ATPase	Chaperones	
X13988	Skeletal muscle myosin heavy chain, member of a family of motor proteins that provide the force for muscle contraction, expressed only during embryogenesis	ATPase	Hydrolase	Cytoplasmic
AB026833	Calcium-sensitive chloride channel, contains five transmembrane domains and displays an outward rectifying conductance of anions, expressed in the lung, trachea, and mammary gland, may be involved in the pathogenesis of cystic fibrosis	Channel [passive transporter]	Transporter	Plasma membrane

Gene Acc	Detailed Description	Enzyme Class	Biological Function	subcellular
AB008775	Aquaporin 9, a water and urea channel expressed predominantly in leukocytes	Channel [passive transporter]	Transporter	Plasma membrane
AB001325	Aquaporin 3, a water channel, member of the MIP family of proteins involved in transport of water, glycerol and other small molecules	Channel [passive transporter]	Transporter	Plasma membrane
L06132	Voltage-dependent anion channel 1 (mitochondrial porin channel), a voltage-gated pore of the outer mitochondrial membrane, mediates apoptotic signals from Bcl2 and related proteins that lead to release of cytochrome c	Channel [passive transporter]	Transporter	Cytoplasmic
U61538	Calcium-binding protein with similarity to calneurin B and calmodulin, binds the sodium-potassium exchanger NHE1, inhibits GTPase-stimulation of NHE1 activity when overexpressed	Channel [passive transporter]	Transporter	
AF026166	Beta subunit of the cytosolic chaperonin containing TCP-1 (CCT), assists in the proper folding of tubulin, actin and contractin, may also be required for the proper folding of Cyclin E	Chaperones		Cytoskeletal
U22662	Member of the nuclear receptor superfamily, forms a heterodimer with the retinoid receptor that makes it responsive to retinoic acid	DNA-binding protein		Nuclear
U22431	Basic helix-loop-helix transcription factor that contains a PAS domain, heterodimerizes with the Ah receptor nuclear translocator (ARNT) and mediates transcriptional responses to hypoxia and dioxin-signaling	DNA-binding protein	Transcription factor	Nuclear
U51903	Protein with GTPase activating domain, multiple-calmodulin binding domains, and actin binding domain, inhibits GTPase activity of Cdc42 and Rac1, which are members of the ras family of GTP binding proteins	GTPase activating protein	Inhibitor or repressor	Cytoskeletal
AF056490	cAMP-specific phosphodiesterase, expressed in testis, ovaries, small intestine, and colon	Hydrolase		

GB Acc	Detailed Description	Enzyme Class	Biological Function	subcellular
J04430	Tartrate-resistant acid phosphatase (purple acid phosphatase, type-5 acid phosphatase), a binuclear, iron-containing phosphatase expressed in monocytes and induced upon monocyte differentiation	Hydrolase	Other phosphatase	
AB020645	Protein with strong similarity to rat Glis, mitochondrial glutaminase, which contains ankyrin (Ank) repeats that may mediate protein-protein interactions	Hydrolase		Mitochondrial
Y08374	Cartilage glycoprotein-39, has similarity to chitinases, expressed in rheumatoid arthritis cartilage and synovial cells	Hydrolase	Structural protein	Extracellular matrix (cuticle and basement membrane)
D55696	Legumain, a cysteine endoprotease that hydrolyzes asparaginyl bonds	Hydrolase	Protease (
X12451	Cathepsin L, a lysosomal cysteine (thiol) protease that cleaves collagen and elastin and is highly expressed in transformed cells	Hydrolase	Protease	Cytoplasmic
U27467	Hemopoietic-specific early-response BCL2-related protein, expression is induced by phorbol ester and inflammatory cytokines, may protect cells during inflammation, required for mitochondrial viability and function	Inhibitor or repressor		
S81221	Lanosterol synthase ((S)-2,3-epoxysqualene mutase), catalyzes the cyclization of (S)-2,3-oxidosqualene to form lanosterol during sterol biosynthesis	Isomerase		
X17025	Isopentenyl diphosphate:dimethylallyl diphosphate isomerase (IPP isomerase), catalyzes the interconversion of isopentenyl diphosphate and dimethylallyl diphosphate in isoprenoid synthesis	Isomerase		Cytoplasmic
AF061741	Short-chain dehydrogenase/reductase, reduces all-trans-retinal during bleached visual pigment regeneration, may function in non-photoreceptor retinol metabolism	Oxidoreductase		Plasma membrane

GB_Acc	Detailed Description	Enzyme Class	Biological Function	subcellular
J03600	5-lipoxygenase, catalyzes the first two steps in the synthesis of leukotrienes, which are involved in allergic and inflammatory responses	Oxidoreductase		Cytoplasmic
AB016247	Protein with similarity to <i>S. cerevisiae</i> Erg3p, which is a sterol-C5-desaturase	Oxidoreductase		
U78294	Arachidonate 15-lipoxygenase, converts arachidonic acid to 15S-hydroperoxyicosatetraenoic acid, poorly metabolizes linoleic acid	Oxidoreductase		
AL050118	Delta-6 desaturase, desaturates 18:2(n-6) and 18:3(n-3) to form 20:4(n-6) (arachidonic acid) and 22:6(n-3) (docosahexaenoic acid)	Oxidoreductase		Plasma membrane
AF034544	7-dehydrocholesterol reductase, removes the C7-8 double bond in 7-dehydrocholesterol; mutations in the corresponding gene cause Smith-Lemli-Opitz syndrome	Oxidoreductase		Cytoplasmic
Y13647	Stearoyl-coenzyme A desaturase, functions in the synthesis of unsaturated fatty acids; upregulated in esophageal and colonic carcinomas and hepatocellular adenoma	Oxidoreductase		
X77094	Component of the cytosolic nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase complex, which is required for the oxidative burst, expressed only in hematopoietic cells	Oxidoreductase		Cytoplasmic
D17793	3 alpha-hydroxysteroid dehydrogenase, oxidizes xenobiotic alicyclic alcohols and 3alpha- or 17beta-hydroxy-5beta-androstanes, activated on exposure to all-trans-retinoic acid, may function in control of cell growth and differentiation	Oxidoreductase Transformation related	Transformation related	
Y12735	Dual-specificity protein kinase	Protein kinase	Transferase	
AF004709	MAP kinase that is activated by stress and proinflammatory cytokines, phosphorylated by MKK6 (PRKMK6)	Protein kinase	Transferaseserine	
X60188	MAP kinase that is activated in response to growth factors	Protein kinase	Transferase	Nuclear

GB Acc	Detailed Description	Enzyme Class	Biological Function	subcellular
L32976	Member of the mixed-lineage kinase family, has SH3 and leucine zipper domains	Protein kinase	Transferase	
X13916	Low density lipoprotein receptor-related protein (alpha-2-macroglobulin receptor), binds to apoE containing lipoproteins and mediates chylomicron remnant clearance from the plasma	Receptor (protein translocation)		Plasma membrane
W60864	Protein with an immunoreceptor tyrosine-based activation motif (ITAM), associates with membrane glycoproteins of the killer-cell inhibitory receptor (KIR) family and activates NK cells	Receptor (signalling)		Plasma membrane
X74039	Urokinase-type plasminogen activator receptor, a member of a superfamily that includes CD59, murine Ly-6, and elapid snake venom toxins, functions in pericellular plasminogen activation	Receptor (signalling)		Plasma membrane
M84562	Lipoxin A4 receptor, a G protein-coupled receptor with similarity to the formyl peptide receptor (FPR1) that binds lipoxins and signals through an inhibitory G-protein to mobilize calcium, stimulates chemotaxis and cell adhesion	Receptor (signalling)		Plasma membrane
D14582	Epimorphin, a signaling protein, has strong similarity to murine Epim and rat Rn.10623; Epim functions in epithelial-mesenchymal interactions, Rn.10623 is involved in docking synaptic vesicles with the presynaptic plasma membrane	Receptor (signalling)		Plasma membrane
M59818	Granulocyte colony-stimulating factor receptor; mutation of the corresponding gene causes severe congenital neutropenia and is also associated with acute myeloid leukemia	Receptor (signalling)		Plasma membrane
U40572	Beta 2-syntrophin, an intracellular membrane-associated protein that binds to dystrophin (DMD), and utrophin/dystrophin related protein	Small molecule-binding protein		Basement membrane (extracellular matrix)

GB Acc	Detailed Description	Enzyme Class	Biological Function	Subcellular
AB006780	Galectin 3, a lactose-binding lectin, involved in cell growth regulation	Small molecule-binding protein		Apical plasma membrane
AJ000414	Protein with an SH3 domain and similarity to the non-kinase domains of FER and Fes/Fps tyrosine kinases, binds to activated Cdc42 and may have a role in regulation of the actin cytoskeleton	Small molecule-binding protein CIP4 is a target for the small GTPase Cdc42		
Z11793	Selenoprotein that contains 10 selenocysteine residues, may function in antioxidant activities	Small molecule-binding protein - Undefined		
U48734	Alpha-actinin, a non-muscle cell actin-binding protein; localization to nucleus in cancer cells is correlated with good prognosis for breast cancer patients	Structural protein		Nuclear
X68733	Alpha-1-antichymotrypsin, a member of the serpin family of serine protease inhibitors; deficiency is associated with lung and liver disease	Structural protein pre-B cell colony enhancement	pre-B cell colony enhancement	
U03644	CBF1-interacting corepressor, links CBF1 and the histone deacetylase complex, binds to histone deacetylase and to SAP30	Transcription factor		
Y09443	Alkyl-dihydroxyacetonephosphate synthase, functions in ether phospholipid biosynthesis, may be deficient in peroxisomal biogenesis disorders Zellweger syndrome, rhizomelic chondrodysplasia punctata, and adrenoleukodystrophy	Transferase		Peroxisome
M58597	Myeloid alpha(1,3)fucosyltransferase (GDP-fucose:[Gal beta 1-4]GlcNAc alpha 1-3-fucosyltransferase), makes the 3-fucosyl-lactosamine epitope (CD15) on polymorphonuclear cells and monocytes, regulates Lex and Ley antigen expression	Transferase		Unspecified membrane
U30930	UDP-galactose ceramide galactosyltransferase, member of the UDP-glucuronosyltransferase 8 family of endoplasmic reticulum glycoproteins that is involved in synthesizing glycosphingolipids, cerebroside and sulfatides, myelin membrane constituents	Transferase		Endoplasmic reticulum

GB_Acc	Detailed Description	Enzyme Class	Biological Function	subcellular
Z35102	Serine/threonine kinase that localizes to the nucleus and is activated via autophosphorylation, expression is ubiquitous	Transferase		Nuclear
L26232	Phospholipid transfer protein, has roles in phospholipid transport and conversion of high density lipoproteins into larger and smaller particles	Transporter		
U41387				
Y08136	Protein of unknown function, has low similarity to a region of acid sphingomyelinases			
AB000220	Semaphorin E, member of a family of proteins involved in neuronal growth cone guidance and immune system regulation, overexpression is associated with resistance to the anticancer drug cis-diamminedichloroplatinum(II), associated with rheumatoid arthritis			
AL034562	Glycosylated receptor-like protein with three immunoglobulin-like domains that probably interacts with phosphotyrosine phosphatases, may have a role in response to growth factors and in cell adhesion			Plasma membrane
U82812	Spalpa, a member of the scavenger receptor cysteine-rich family that is expressed in lymphoid tissues and may be involved in the regulation of monocyte activation, function, and survival			Extracellular (excluding cell wall)
AL034562	Glycosylated receptor-like protein with three immunoglobulin-like domains that probably interacts with phosphotyrosine phosphatases, may have a role in response to growth factors and in cell adhesion			Plasma membrane
S60099				
H24861				
AF089750	Protein with very strong similarity to murine Mm.2931 (flotillin), which is an integral membrane protein of caveolae that is expressed in brain			Plasma membrane

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GB Acc	Detailed Description	Enzyme Class	Biological Function	subcellular
AF001383	Amphiphysin II, a tumor suppressor that interacts with MYC and colocalizes with ankyrin3 (ANK3), may have a role in endocytosis			Cytoplasmic
U69274				
U49392	Allograft inflammatory factor 1, cytokine inducible protein associated with vascular injury			Nuclear
AF035284				

CLAIMS

1. A method for the prediction, diagnosis or prognosis of a cardiovascular
5 disease by the detection of:
- a) a polynucleotide comprising at least one of the sequences of SEQ ID
NO. 1 to 74;
 - 10 b) a polynucleotide which hybridises under stringent conditions to a
polynucleotide specified in (a) and encodes a polypeptide exhibiting
the same biological function as specified for the respective sequence
in the Tables 1 and 2;
 - 15 c) a polynucleotide the sequence of which deviates from the poly-
nucleotide specified in (a) and (b) due to the generation of the genetic
code and encodes a polypeptide exhibiting the same biological
function as specified for the respective sequence in the Tables 1 and 2;
 - 20 d) a polynucleotide which represents a specific fragment, derivative or
allelic variation of a polynucleotide sequence specified in (a) to (c)
and encodes a polypeptide exhibiting the same biological function as
specified for the respective sequence in the Tables 1 and 2;
- 25 in a biological sample comprising the following steps:
- hybridising at least one polynucleotide specified in (a) to (d) to a nucleic
acid material of a biological sample, thereby forming a hybridization
complex; and
- 30 detecting said hybridization complex.

2. The method of claim 1, wherein before hybridization, the nucleic acid material of the biological sample is amplified.
- 5 3. A method for the prediction, diagnosis or prognosis of a cardiovascular disease by the detection of:
- 10 a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;
- b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 15 c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 20 d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 25 e) a polypeptide encoded by a polynucleotide sequence specified in (a) to (d) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 30 f) a purified polypeptide comprising at least one of the sequences of SEQ ID NO. 75 to 147;

comprising the step of contacting a biological sample with a reagent which specifically interacts with the polynucleotide specified in (a) to (d) or the polypeptide specified in (e) and (f).

5

4. A diagnostic kit for conducting the method of any of claims 1 to 3.
5. A composition for the prediction, diagnosis or prognosis of cardiovascular disease comprising a detection agent for:

10

- a) any polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;

15

- b) any polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

20

- c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

25

- d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

30

- e) a polypeptide encoded by a polynucleotide sequence specified in (a) to (d);

- f) a polypeptide comprising at least one of the sequences of SEQ ID NO. 75 to 147.
6. An array comprising a plurality of polynucleotides wherein each of the polynucleotides is selected from:
- a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;
- b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c);
- attached to a solid support.
7. A method of screening for agents which regulate the activity of a polypeptide encoded by a polynucleotide selected from the group consisting of:
- a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;

b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

5

c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

10

d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

15

comprising the steps of:

contacting a test compound with at least one polypeptide encoded by a polynucleotide specified in (a) to (d); and

20

detecting binding of the test compound to the polypeptide, wherein a test compound which binds to the polypeptide is identified as a potential therapeutic agent for modulating the activity of the polypeptide in order to prevent or treat a cardiovascular disease.

25

8. A method of screening for agents which regulate the activity of a polypeptide encoded by a polynucleotide selected from the group consisting of:

a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;

30

b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

5

c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

10

d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

15

comprising the steps of:

contacting a test compound with at least one polypeptide encoded by a polynucleotide specified in (a) to (d); and

20

detecting the activity of the polypeptide as specified for the respective sequence in the Tables 1 and 2, wherein a test compound which increases the activity is identified as a potential preventive or therapeutic agent for increasing the activity in a cardiovascular disease, and wherein a test compound which decreases the activity of the polypeptide is identified as a potential therapeutic agent for decreasing the activity in a cardiovascular disease.

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9. A method of screening for agents which regulate the activity of a polynucleotide selected from group consisting of;

- 5
- a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;
- b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 10
- c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 15
- d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

comprising the steps of:

20

contacting a test compound with at least one polynucleotide specified in (a) to (d), and

25

detecting binding of the test compound to the polynucleotide, wherein a test compound which binds to the polynucleotide is identified as a potential preventive or therapeutic agent for regulating the activity of the polynucleotide in a cardiovascular disease.

30

10. Use of

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- 5
- a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;
- b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 10
- c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 15
- d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c);
- e) an antisense molecule targeting one of the polynucleotide sequences specified in (a) to (d);
- 20
- f) a purified polypeptide encoded by a polynucleotide sequence specified in (a) to (d)
- g) a purified polypeptide comprising at least one of the sequences of SEQ ID NO. 75 to 147;
- 25
- h) an antibody capable of binding to one of the polynucleotide specified in (a) to (d) or a polypeptide specified in (f) and (g)
- 30
- i) a reagent identified by any of the methods of claim 7 to 9 that modulates the amount or activity of a polynucleotide sequence specified in (a) to (d) or a polypeptide specified in (f) and (g)

for the preparation of compositions for the prevention, prediction, diagnosis, prognosis or a medicament for the treatment of a cardiovascular disease.

- 5 11. Use of claim 10 wherein the disease is atherosclerosis.
12. A reagent that regulates the activity of a polynucleotide selected from the group consisting of:
- 10 a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;
- 15 b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 20 c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 25 d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;
- 30 e) or a polypeptide encoded by at least one of the polynucleotides specified in (a) to (d);

wherein said reagent is identified by the method of any of the claims 7 to 9.

13. A pharmaceutical composition, comprising:

an expression vector containing at least one polynucleotide selected from the group consisting of:

a) a polynucleotide comprising at least one of the sequences of SEQ ID NO. 1 to 74;

b) a polynucleotide which hybridises under stringent conditions to a polynucleotide specified in (a) encoding a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

c) a polynucleotide the sequence of which deviates from the polynucleotide specified in (a) and (b) due to the generation of the genetic code and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

d) a polynucleotide which represents a specific fragment, derivative or allelic variation of a polynucleotide sequence specified in (a) to (c) and encodes a polypeptide exhibiting the same biological function as specified for the respective sequence in the Tables 1 and 2;

or the reagent of claim 12 and a pharmaceutically acceptable carrier.

14. A computer-readable medium comprising at least one digitally encoded value representing a level of expression of at least one polynucleotide sequence of SEQ ID NO. 1 to 74 in a cell from the a subject at risk for or having cardiovascular disease.

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<213> Homo sapiens

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<211> 5767

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 19

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<211> 1850

<212> DNA

<213> Homo sapiens

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<211> 1575

<212> DNA

<213> Homo sapiens

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<211> 737

<212> DNA

<213> Homo sapiens

<400> 22

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<210> 23

<211> 2637

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 1401

<212> DNA

<213> Homo sapiens

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<211> 2497

<212> DNA

<213> Homo sapiens

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<211> 2125

<212> DNA

<213> Homo sapiens

<400> 27

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<211> 2685

<212> DNA

<213> Homo sapiens

<400> 28

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<211> 2621

<212> DNA

<213> Homo sapiens

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<211> 2153

<212> DNA

<213> Homo sapiens

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<211> 1245

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

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<211> 1838

<212> DNA

<213> Homo sapiens

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<210> 36

<211> 1866

<212> DNA

<213> Homo sapiens

<400> 36

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<211> 14896

<212> DNA

<213> Homo sapiens

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- 68 -

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<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 43

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<212> DNA

<213> Homo sapiens

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<212> DNA

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<210> 47

<211> 2038

<212> DNA

<213> Homo sapiens

<400> 47

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<210> 48

<211> 3474

<212> DNA

<213> Homo sapiens

<400> 48

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<211> 1466

<212> DNA

<213> Homo sapiens

<400> 49

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<210> 50

<211> 1519

<212> DNA

<213> Homo sapiens

<400> 50

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- 82 -

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<211> 2074

<212> DNA

<213> Homo sapiens

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- 83 -

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<210> 52

<211> 2861

<212> DNA

<213> Homo sapiens

<400> 52

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<212> DNA

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<211> 2143

<212> DNA

<213> Homo sapiens

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<211> 1806

<212> DNA

<213> Homo sapiens

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<212> DNA

<213> Homo sapiens

<400> 67

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<210> 69

<211> 660

<212> DNA

<213> Homo sapiens

<400> 69

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<211> 3257

<212> DNA

<213> Homo sapiens

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3257

<210> 71

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<212> DNA

<213> Homo sapiens

<400> 71

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<210> 72

<211> 3992

<212> DNA

<213> Homo sapiens

<400> 72

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<210> 73

<211> 1490

<212> DNA

<213> Homo sapiens

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ccagatgatc tgtgggtcag gcctaaaagc tgtgtgcctt gcagtccagt caatagggat 360
aggagactcc agcattgtgg ttgcaggagg catggaaaat atgagcaagg ctctcactt 420
ggcttacttg agaacaggag taaagatagg tgagatgcca ctgactgaca gtatactctg 480
tgatggtctt acagatgcat ttcacaactg tcatatgggt attacagctg aaaatgtagc 540
cacaaaatgg caagttagta gagaagatca ggacaagggt gcagttctgt ccagaacag 600

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gacagagaat gcacagaaaag ctggccattt tgacaaagag attgtaccag ttttggtgtc 660
aactagaaaa ggtctttattg aagttaaaac agatgagttt cctcgccatg ggagcaacat 720
agaagccatg tccaagctaa agccttactt tcttactgat ggaacgggaa cagtcacccc 780
agccaatgct tcaggaataa atgatggtgc tgcagctggt gctcttatga agaagtcaga 840
agctgataaa cgtgggctta caccttttagc acggatagtt tcctgggtccc aagtgggtgt 900
ggagccttcc attatgggaa taggaccaat tccagccata aagcaagctg ttacaaaagc 960
aggttggtca ctggaagatg ttgacatatt tgaaatcaat gaagcctttg cagctgtctc 1020
tgctgcaata gttaaagaac ttggattaaa cccagagaag gtcaatattg aaggaggggc 1080
tatagccttg ggccaccctc ttggagcatc tggctgtcga attcttgtga cctgtttaca 1140
cacactggag agaatgggca gaagtcgtgg tgttgagcc ctgtgcattg ggggtgggat 1200
gggaatagca atgtgtgttc agagagaatg acaatgtgtg ttcagagaga atgaattgct 1260
taaactttga acaacctcaa tttcttttta aactaataaa gtactagggt gcaatatgtg 1320
aaatcagagg accaaagtac agatggaaac catttcctac atcacaaaaa cccaagttta 1380
cagcttgtac tttactttaa tgtgtaatac tcaactcacg gtacaagaca attgcattta 1440
acattgttat aaataaaag aacatcagat caatcattaa aaaaaaaaaa 1490

```

<210> 74

<211> 1339

<212> DNA

<213> Homo sapiens

<400> 74

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ttgcactcta gaagggacaa tggacttctg gctttggcca ctttaacttc tgccagtatc 60
gggggccctg aggatcctcc cagaagtaaa ggtagagggg gagctgggag gatcagttac 120
catcaagtgc ccacttctcg aaatgcatgt gaggatatat ctgtgccggg agatggctgg 180
atctggaaca tgtggtaccg tggtatccac caccaacttc atcaaggcag aatacaaggg 240
ccgagttact ctgaagcaat acccagcaa gaatctgttc ctagtggagg taacacagct 300
gacagaaaag gacagcggag tctatgcctg cggagcgggc atgaacacag accggggaaa 360
gaccagaaa gtcaccctga atgtccacag tgaatacag ccatcatggg aagagcagcc 420
aatgcctgag actccaaaat ggtttcatct gccctatttg ttccagatgc ctgcatatgc 480
cagttcttcc aaattcgtaa ccagagttac cacaccagct caaaggggca aggtccctcc 540

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```

agttcaccac tcttccccca ccacccaaat caccaccgc cctcgagtgt ccagagcatc 600
ttcagtagca ggtgacaagc cccgaacctt cctgccatcc actacagcct caaaaatctc 660
agctctggag gggctgctca agccccagac gccagctac aaccaccaca ccaggctgca 720
caggcagaga gcactggact atggctcaca gtctgggagg gaaggccaag gatttcacat 780
cctgatcccg accatcctgg gccttttctt gctgggaactt ctggggctgg tggtgaaaag 840
ggccgttgaa aggaggaaaag cctctccag gcggggccgc cgactggccg tgaggatgcg 900
cgccctggag agtcccaga ggccccgcgg gtcgcgcga ccgcgctccc aaaacaacat 960
ctacagcgcc tgccccgggc gcgctcgtgg agcggacgct gcaggcacag gggaagcccc 1020
cgttcccgcc cccggagcgc cgttgccccc cgccccgctg cagggtgtctg aatctccctg 1080
gctccatgcc ccattctctga agaccagctg tgaatacgtg agcctctacc accagcctgc 1140
cgccatgatg gaggacagtg attcagatga ctacatcaat gttcctgcct gacaaactccc 1200
cagctatccc ccaaccccag gctoggactg tggtgccaag gagtctcatc tatctgctga 1260
tgtccaatac ctgcttcatt tgttctcaga gccctcatca ttcccatgcc ccattctgat 1320
cccatcccca tctatctgt 1339

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<210> 75

<211> 152

<212> PRT

<213> Homo sapiens

<400> 75

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Met Ala Asn Leu Glu Arg Thr Phe Ile Ala Ile Lys Pro Asp Gly Val
1           5           10          15

```

```

Gln Arg Gly Leu Val Gly Glu Ile Ile Lys Arg Phe Glu Gln Lys Gly
20           25          30

```

```

Phe Arg Leu Val Ala Met Lys Phe Leu Arg Ala Ser Glu Glu His Leu
35           40          45

```

```

Lys Gln His Tyr Ile Asp Leu Lys Asp Arg Pro Phe Phe Pro Gly Leu
50           55          60

```

```

Val Lys Tyr Met Asn Ser Gly Pro Val Val Ala Met Val Trp Glu Gly

```

- 120 -

65 70 75 80

Leu Asn Val Val Lys Thr Gly Arg Val Met Leu Gly Glu Thr Asn Pro
 85 90 95

Ala Asp Ser Lys Pro Gly Thr Ile Arg Gly Asp Phe Cys Ile Gln Val
 100 105 110

Gly Arg Asn Ile Ile His Gly Ser Asp Ser Val Lys Ser Ala Glu Lys
 115 120 125

Glu Ile Ser Leu Trp Phe Lys Pro Glu Glu Leu Val Asp Tyr Lys Ser
 130 135 140

Cys Ala His Asp Trp Val Tyr Glu
 145 150

<210> 76

<211> 538

<212> PRT

<213> Homo sapiens

<400> 76

Gly Asn Ser Ile Ser Leu Asp Phe Glu Pro Ser Ile Glu Tyr Gln Phe
 1 5 10 15

Val Glu Arg Leu Glu Glu Arg Tyr Lys Cys Ala Phe Cys His Ser Val
 20 25 30

Leu His Asn Pro His Gln Thr Gly Cys Gly His Arg Phe Cys Gln His
 35 40 45

Cys Ile Leu Ser Leu Arg Glu Leu Asn Thr Val Pro Ile Cys Pro Val
 50 55 60

Asp Lys Glu Val Ile Lys Ser Gln Glu Val Phe Lys Asp Asn Cys Cys
 65 70 75 80

Lys Arg Glu Val Leu Asn Leu Tyr Val Tyr Cys Ser Asn Ala Pro Gly
 85 90 95

- 121 -

Cys Asn Ala Lys Val Ile Leu Gly Arg Tyr Gln Asp His Leu Gln Gln
 100 105 110

Cys Leu Phe Gln Pro Val Gln Cys Ser Asn Glu Lys Cys Arg Glu Pro
 115 120 125

Val Leu Arg Lys Asp Leu Lys Glu His Leu Ser Ala Ser Cys Gln Phe
 130 135 140

Arg Lys Glu Lys Cys Leu Tyr Cys Lys Lys Asp Val Val Val Ile Asn
 145 150 155 160

Leu Gln Asn His Glu Glu Asn Leu Cys Pro Glu Tyr Pro Val Phe Cys
 165 170 175

Pro Asn Asn Cys Ala Lys Ile Ile Leu Lys Thr Glu Val Asp Glu His
 180 185 190

Leu Ala Val Cys Pro Glu Ala Glu Gln Asp Cys Pro Phe Lys His Tyr
 195 200 205

Gly Cys Ala Val Thr Asp Lys Arg Arg Asn Leu Gln Gln His Glu His
 210 215 220

Ser Ala Leu Arg Glu His Met Arg Leu Val Leu Glu Lys Asn Val Gln
 225 230 235 240

Leu Glu Glu Gln Ile Ser Asp Leu His Lys Ser Leu Glu Gln Lys Glu
 245 250 255

Ser Lys Ile Gln Gln Leu Ala Glu Thr Ile Lys Lys Leu Glu Lys Glu
 260 265 270

Phe Lys Gln Phe Ala Gln Leu Phe Gly Lys Asn Gly Ser Phe Leu Pro
 275 280 285

Asn Ile Gln Val Phe Ala Ser His Ile Asp Lys Ser Ala Trp Leu Glu
 290 295 300

Ala Gln Val His Gln Leu Leu Gln Met Val Asn Gln Gln Gln Asn Lys
 305 310 315 320

Phe Asp Leu Arg Pro Leu Met Glu Ala Val Asp Thr Val Lys Gln Lys
 325 330 335

- 122 -

Ile Thr Leu Leu Glu Asn Asn Asp Gln Arg Leu Ala Val Leu Glu Glu
 340 345 350

Glu Thr Asn Lys His Asp Thr His Ile Asn Ile His Lys Ala Gln Leu
 355 360 365

Ser Lys Asn Glu Glu Arg Phe Lys Leu Leu Glu Gly Thr Cys Tyr Asn
 370 375 380

Gly Lys Leu Ile Trp Lys Val Thr Asp Tyr Lys Met Lys Lys Arg Glu
 385 390 395 400

Ala Val Asp Gly His Thr Val Ser Ile Phe Ser Gln Ser Phe Tyr Thr
 405 410 415

Ser Arg Cys Gly Tyr Arg Leu Cys Ala Arg Ala Tyr Leu Asn Gly Asp
 420 425 430

Gly Ser Gly Arg Gly Ser His Leu Ser Leu Tyr Phe Val Val Met Arg
 435 440 445

Gly Glu Phe Asp Ser Leu Leu Gln Trp Pro Phe Arg Gln Arg Val Thr
 450 455 460

Leu Met Leu Leu Asp Gln Ser Gly Lys Lys Asn Ile Met Glu Thr Phe
 465 470 475 480

Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Arg Pro Asp Gly Glu Met
 485 490 495

Asn Ile Ala Ser Gly Cys Pro Arg Phe Val Ala His Ser Val Leu Glu
 500 505 510

Asn Ala Lys Asn Ala Tyr Ile Lys Asp Asp Thr Leu Phe Leu Lys Val
 515 520 525

Ala Val Asp Leu Thr Asp Leu Glu Asp Leu
 530 535

<210> 77

<211> 583

<212> PRT

- 123 -

<213> Homo sapiens

<400> 77

Met Pro Lys Pro Ile Asn Val Arg Val Thr Thr Met Asp Ala Glu Leu
 1 5 10 15

Glu Phe Ala Ile Gln Pro Asn Thr Thr Gly Lys Gln Leu Phe Asp Gln
 20 25 30

Val Val Lys Thr Val Gly Leu Arg Glu Val Trp Phe Phe Gly Leu Gln
 35 40 45

Tyr Val Asp Ser Lys Gly Tyr Ser Thr Trp Leu Lys Leu Asn Lys Lys
 50 55 60

Val Thr Gln Gln Asp Val Lys Lys Glu Asn Pro Leu Gln Phe Lys Phe
 65 70 75 80

Arg Ala Lys Phe Phe Pro Glu Asp Val Ser Glu Glu Leu Ile Gln Glu
 85 90 95

Ile Thr Gln Arg Leu Phe Phe Leu Gln Val Lys Glu Ala Ile Leu Asn
 100 105 110

Asp Glu Ile Tyr Cys Pro Pro Glu Thr Ala Val Leu Leu Ala Ser Tyr
 115 120 125

Ala Val Gln Ala Lys Tyr Gly Asp Tyr Asn Lys Glu Ile His Lys Pro
 130 135 140

Gly Tyr Leu Ala Asn Asp Arg Leu Leu Pro Gln Arg Val Leu Glu Gln
 145 150 155 160

His Lys Leu Thr Lys Glu Gln Trp Glu Glu Arg Ile Gln Asn Trp His
 165 170 175

Glu Glu His Arg Gly Met Leu Arg Glu Asp Ser Met Met Glu Tyr Leu
 180 185 190

Lys Ile Ala Gln Asp Leu Glu Met Tyr Gly Val Asn Tyr Phe Glu Ile
 195 200 205

Lys Asn Lys Lys Gly Thr Glu Leu Trp Leu Gly Val Asp Ala Leu Gly

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210	215	220
Leu Asn Ile Tyr Glu His Asp Asp Lys Leu Thr Pro Lys Ile Gly Phe 225 230 235 240		
Pro Trp Ser Glu Ile Arg Asn Ile Ser Phe Asn Asp Lys Lys Phe Val 245 250 255		
Ile Lys Pro Ile Asp Lys Lys Ala Pro Asp Phe Val Phe Tyr Ala Pro 260 265 270		
Arg Leu Arg Ile Asn Lys Arg Ile Leu Ala Leu Cys Met Gly Asn His 275 280 285		
Glu Leu Tyr Met Arg Arg Arg Lys Pro Asp Thr Ile Glu Val Gln Gln 290 295 300		
Met Lys Ala Gln Ala Arg Glu Glu Lys His Gln Lys Gln Leu Glu Arg 305 310 315 320		
Ala Gln Leu Glu Asn Glu Lys Lys Lys Arg Glu Ile Ala Glu Lys Glu 325 330 335		
Lys Glu Arg Ile Glu Arg Glu Lys Glu Glu Leu Met Glu Arg Leu Lys 340 345 350		
Gln Ile Glu Glu Gln Thr Ile Lys Ala Gln Lys Glu Leu Glu Glu Gln 355 360 365		
Thr Arg Lys Ala Leu Glu Leu Asp Gln Glu Arg Lys Arg Ala Lys Glu 370 375 380		
Glu Ala Glu Arg Leu Glu Lys Glu Arg Arg Ala Ala Glu Glu Ala Lys 385 390 395 400		
Ser Ala Ile Ala Lys Gln Ala Ala Asp Gln Met Lys Asn Gln Glu Gln 405 410 415		
Leu Ala Ala Glu Leu Ala Glu Phe Thr Ala Lys Ile Ala Leu Leu Glu 420 425 430		
Glu Ala Lys Lys Lys Lys Glu Glu Glu Ala Thr Glu Trp Gln His Lys 435 440 445		

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Ala Phe Ala Ala Gln Glu Asp Leu Glu Lys Thr Lys Glu Glu Leu Lys
 450 455 460

Thr Val Met Ser Ala Pro Pro Pro Pro Pro Pro Pro Pro Val Ile Pro
 465 470 475 480

Pro Thr Glu Asn Glu His Asp Glu His Asp Glu Asn Asn Ala Glu Ala
 485 490 495

Ser Ala Glu Leu Ser Asn Glu Gly Val Met Asn His Arg Ser Glu Glu
 500 505 510

Glu Arg Val Thr Glu Thr Gln Lys Asn Glu Arg Val Lys Lys Gln Leu
 515 520 525

Gln Ala Leu Ser Ser Glu Leu Ala Gln Ala Arg Asp Glu Thr Lys Lys
 530 535 540

Thr Gln Asn Asp Val Leu His Ala Glu Asn Val Lys Ala Gly Arg Asp
 545 550 555 560

Lys Tyr Lys Thr Leu Arg Gln Ile Arg Gln Gly Asn Thr Lys Gln Arg
 565 570 575

Ile Asp Glu Phe Glu Ala Met
 580

<210> 78

<211> 580

<212> PRT

<213> Homo sapiens

<400> 78

Met Asn Phe Leu Arg Arg Arg Leu Ser Asp Ser Ser Phe Met Ala Asn
 1 5 10 15

Leu Pro Asn Gly Tyr Met Thr Asp Leu Gln Arg Pro Asp Ser Ser Thr
 20 25 30

Ser Ser Pro Ala Ser Pro Ala Met Glu Arg Arg His Pro Gln Pro Leu
 35 40 45

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Ala Ala Ser Phe Ser Ser Pro Gly Ser Ser Leu Phe Ser Ser Leu Ser
50 55 60

Ser Ala Met Lys Gln Ala Pro Gln Ala Thr Ser Gly Leu Met Glu Pro
65 70 75 80

Pro Gly Pro Ser Thr Pro Ile Val Gln Arg Pro Arg Ile Leu Leu Val
85 90 95

Ile Asp Asp Ala His Thr Asp Trp Ser Lys Tyr Phe His Gly Lys Lys
100 105 110

Val Asn Gly Glu Ile Glu Ile Arg Val Glu Gln Ala Glu Phe Ser Glu
115 120 125

Leu Asn Leu Ala Ala Tyr Val Thr Gly Gly Cys Met Val Asp Met Gln
130 135 140

Val Val Arg Asn Gly Thr Lys Val Val Ser Arg Ser Phe Lys Pro Asp
145 150 155 160

Phe Ile Leu Val Arg Gln His Ala Tyr Ser Met Ala Leu Gly Glu Asp
165 170 175

Tyr Arg Ser Leu Val Ile Gly Leu Gln Tyr Gly Gly Leu Pro Ala Val
180 185 190

Asn Ser Leu Tyr Ser Val Tyr Asn Phe Cys Ser Lys Pro Trp Val Phe
195 200 205

Ser Gln Leu Ile Lys Ile Phe His Ser Leu Gly Pro Glu Lys Phe Pro
210 215 220

Leu Val Glu Gln Thr Phe Phe Pro Asn His Lys Pro Met Val Thr Ala
225 230 235 240

Pro His Phe Pro Val Val Val Lys Leu Gly His Ala His Ala Gly Met
245 250 255

Gly Lys Ile Lys Val Glu Asn Gln Leu Asp Phe Gln Asp Ile Thr Ser
260 265 270

Val Val Ala Met Ala Lys Thr Tyr Ala Thr Thr Glu Ala Phe Ile Asp
275 280 285

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Ser Lys Tyr Asp Ile Arg Ile Gln Lys Ile Gly Ser Asn Tyr Lys Ala
 290 295 300

Tyr Met Arg Thr Ser Ile Ser Gly Asn Trp Lys Ala Asn Thr Gly Ser
 305 310 315 320

Ala Met Leu Glu Gln Val Ala Met Thr Glu Arg Tyr Arg Leu Trp Val
 325 330 335

Asp Ser Cys Ser Glu Met Phe Gly Gly Leu Asp Ile Cys Ala Val Lys
 340 345 350

Ala Val His Ser Lys Asp Gly Arg Asp Tyr Ile Ile Glu Val Met Asp
 355 360 365

Ser Ser Met Pro Leu Ile Gly Glu His Val Glu Glu Asp Arg Gln Leu
 370 375 380

Met Ala Asp Leu Val Val Ser Lys Met Ser Gln Leu Pro Met Pro Gly
 385 390 395 400

Gly Thr Ala Pro Ser Pro Leu Arg Pro Trp Ala Pro Gln Ile Lys Ser
 405 410 415

Ala Lys Ser Pro Gly Gln Ala Gln Leu Gly Pro Gln Leu Gly Gln Pro
 420 425 430

Gln Pro Arg Pro Pro Pro Gln Gly Gly Pro Arg Gln Ala Gln Ser Pro
 435 440 445

Gln Pro Gln Arg Ser Gly Ser Pro Ser Gln Gln Arg Leu Ser Pro Gln
 450 455 460

Gly Gln Gln Pro Leu Ser Pro Gln Ser Gly Ser Pro Gln Gln Gln Arg
 465 470 475 480

Ser Pro Gly Ser Pro Gln Leu Ser Arg Ala Ser Ser Gly Ser Ser Pro
 485 490 495

Asn Gln Ala Ser Lys Pro Gly Ala Thr Leu Ala Ser Gln Pro Arg Pro
 500 505 510

Pro Val Gln Gly Arg Ser Thr Ser Gln Gln Gly Glu Glu Ser Lys Lys

- 128 -

515 520 525
 Pro Ala Pro Pro His Pro His Leu Asn Lys Ser Gln Ser Leu Thr Asn
 530 535 540
 Ser Leu Ser Thr Ser Asp Thr Ser Gln Arg Gly Thr Pro Ser Glu Asp
 545 550 555 560
 Glu Ala Lys Ala Glu Thr Ile Arg Asn Leu Arg Lys Ser Phe Ala Ser
 565 570 575
 Leu Phe Ser Asp
 580

<210> 79

<211> 641

<212> PRT

<213> Homo sapiens

<400> 79

Met Ala Lys Ala Ala Ala Ile Gly Ile Asp Leu Gly Thr Thr Tyr Ser
 1 5 10 15
 Cys Val Gly Val Phe Gln His Gly Lys Val Glu Ile Ile Ala Asn Asp
 20 25 30
 Gln Gly Asn Arg Thr Thr Pro Ser Tyr Val Ala Phe Thr Asp Thr Glu
 35 40 45
 Arg Leu Ile Gly Asp Ala Ala Lys Asn Gln Val Ala Leu Asn Pro Gln
 50 55 60
 Asn Thr Val Phe Asp Ala Lys Arg Leu Ile Gly Arg Lys Phe Gly Asp
 65 70 75 80
 Pro Val Val Gln Ser Asp Met Lys His Trp Pro Phe Gln Val Ile Asn
 85 90 95
 Asp Gly Asp Lys Pro Lys Val Gln Val Ser Tyr Lys Gly Glu Thr Lys
 100 105 110

- 129 -

Ala Phe Tyr Pro Glu Glu Ile Ser Ser Met Val Leu Thr Lys Met Lys
 115 120 125

Glu Ile Ala Glu Ala Tyr Leu Gly Tyr Pro Val Thr Asn Ala Val Ile
 130 135 140

Thr Val Pro Ala Tyr Phe Asn Asp Ser Gln Arg Gln Ala Thr Lys Asp
 145 150 155 160

Ala Gly Val Ile Ala Gly Leu Asn Val Leu Arg Ile Ile Asn Glu Pro
 165 170 175

Thr Ala Ala Ala Ile Ala Tyr Gly Leu Asp Arg Thr Gly Lys Gly Glu
 180 185 190

Arg Asn Val Leu Ile Phe Asp Leu Gly Gly Gly Thr Phe Asp Val Ser
 195 200 205

Ile Leu Thr Ile Asp Asp Gly Ile Phe Glu Val Lys Ala Thr Ala Gly
 210 215 220

Asp Thr His Leu Gly Gly Glu Asp Phe Asp Asn Arg Leu Val Asn His
 225 230 235 240

Phe Val Glu Glu Phe Lys Arg Lys His Lys Lys Asp Ile Ser Gln Asn
 245 250 255

Lys Arg Ala Val Arg Arg Leu Arg Thr Ala Cys Glu Arg Ala Lys Arg
 260 265 270

Thr Leu Ser Ser Ser Thr Gln Ala Ser Leu Glu Ile Asp Ser Leu Phe
 275 280 285

Glu Gly Ile Asp Phe Tyr Thr Ser Ile Thr Arg Ala Arg Phe Glu Glu
 290 295 300

Leu Cys Ser Asp Leu Phe Arg Ser Thr Leu Glu Pro Val Glu Lys Ala
 305 310 315 320

Leu Arg Asp Ala Lys Leu Asp Lys Ala Gln Ile His Asp Leu Val Leu
 325 330 335

Val Gly Gly Ser Thr Arg Ile Pro Lys Val Gln Lys Leu Leu Gln Asp
 340 345 350

- 130 -

Phe Phe Asn Gly Arg Asp Leu Asn Lys Ser Ile Asn Pro Asp Glu Ala
 355 360 365

Val Ala Tyr Gly Ala Ala Val Gln Ala Ala Ile Leu Met Gly Asp Lys
 370 375 380

Ser Glu Asn Val Gln Asp Leu Leu Leu Leu Asp Val Ala Pro Leu Ser
 385 390 395 400

Leu Gly Leu Glu Thr Ala Gly Gly Val Met Thr Ala Leu Ile Lys Arg
 405 410 415

Asn Ser Thr Ile Pro Thr Lys Gln Thr Gln Ile Phe Thr Thr Tyr Ser
 420 425 430

Asp Asn Gln Pro Gly Val Leu Ile Gln Val Tyr Glu Gly Glu Arg Ala
 435 440 445

Met Thr Lys Asp Asn Asn Leu Leu Gly Arg Phe Glu Leu Ser Gly Ile
 450 455 460

Pro Pro Ala Pro Arg Gly Val Pro Gln Ile Glu Val Thr Phe Asp Ile
 465 470 475 480

Asp Ala Asn Gly Ile Leu Asn Val Thr Ala Thr Asp Lys Ser Thr Gly
 485 490 495

Lys Ala Asn Lys Ile Thr Ile Thr Asn Asp Lys Gly Arg Leu Ser Lys
 500 505 510

Glu Glu Ile Glu Arg Met Val Gln Glu Ala Glu Lys Tyr Lys Ala Glu
 515 520 525

Asp Glu Val Gln Arg Glu Arg Val Ser Ala Lys Asn Ala Leu Glu Ser
 530 535 540

Tyr Ala Phe Asn Met Lys Ser Ala Val Glu Asp Glu Gly Leu Lys Gly
 545 550 555 560

Lys Ile Ser Glu Ala Asp Lys Lys Lys Val Leu Asp Lys Cys Gln Glu
 565 570 575

Val Ile Ser Trp Leu Asp Ala Asn Thr Leu Ala Glu Lys Asp Glu Phe
 580 585 590

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Glu His Lys Arg Lys Glu Leu Glu Gln Val Cys Asn Pro Ile Ile Ser
 595 600 605

Gly Leu Tyr Gln Gly Ala Gly Gly Pro Gly Pro Gly Gly Phe Gly Ala
 610 615 620

Gln Gly Pro Lys Gly Gly Ser Gly Ser Gly Pro Thr Ile Glu Glu Val
 625 630 635 640

Asp

<210> 80

<211> 1940

<212> PRT

<213> Homo sapiens

<400> 80

Met Ser Ser Asp Thr Glu Met Glu Val Phe Gly Ile Ala Ala Pro Phe
 1 5 10 15

Leu Arg Lys Ser Glu Lys Glu Arg Ile Glu Ala Gln Asn Gln Pro Phe
 20 25 30

Asp Ala Lys Thr Tyr Cys Phe Val Val Asp Ser Lys Glu Glu Tyr Ala
 35 40 45

Lys Gly Lys Ile Lys Ser Ser Gln Asp Gly Lys Val Thr Val Glu Thr
 50 55 60

Glu Asp Asn Arg Thr Leu Val Val Lys Pro Glu Asp Val Tyr Ala Met
 65 70 75 80

Asn Pro Pro Lys Phe Asp Arg Ile Glu Asp Met Ala Met Leu Thr His
 85 90 95

Leu Asn Glu Pro Ala Val Leu Tyr Asn Leu Lys Asp Arg Tyr Thr Ser
 100 105 110

Trp Met Ile Tyr Thr Tyr Ser Gly Leu Phe Cys Val Thr Val Asn Pro

- 132 -

115	120	125
Tyr Lys Trp Leu Pro Val	Tyr Asn Pro Glu Val Val	Glu Gly Tyr Arg
130	135	140
Gly Lys Lys Arg Gln Glu Ala Pro Pro His Ile Phe Ser Ile Ser Asp		
145	150	155 160
Asn Ala Tyr Gln Phe Met Leu Thr Asp Arg Glu Asn Gln Ser Ile Leu		
	165 170	175
Ile Thr Gly Glu Ser Gly Ala Gly Lys Thr Val Asn Thr Lys Arg Val		
	180 185	190
Ile Gln Tyr Phe Ala Thr Ile Ala Ala Thr Gly Asp Leu Ala Lys Lys		
	195 200	205
Lys Asp Ser Lys Met Lys Gly Thr Leu Glu Asp Gln Ile Ile Ser Ala		
	210 215	220
Asn Pro Leu Leu Glu Ala Phe Gly Asn Ala Lys Thr Val Arg Asn Asp		
	225 230	235 240
Asn Ser Ser Arg Phe Gly Lys Phe Ile Arg Ile His Phe Gly Thr Thr		
	245 250	255
Gly Lys Leu Ala Ser Ala Asp Ile Glu Thr Tyr Leu Leu Glu Lys Ser		
	260 265	270
Arg Val Thr Phe Gln Leu Lys Ala Glu Arg Ser Tyr His Ile Phe Tyr		
	275 280	285
Gln Ile Leu Ser Asn Lys Lys Pro Glu Leu Ile Glu Leu Leu Leu Ile		
	290 295	300
Thr Thr Asn Pro Tyr Asp Tyr Pro Phe Ile Ser Gln Gly Glu Ile Leu		
	305 310	315 320
Val Ala Ser Ile Asp Asp Arg Glu Glu Leu Leu Ala Thr Asp Ser Ala		
	325 330	335
Ile Asp Ile Leu Gly Phe Thr Pro Glu Glu Lys Ser Gly Leu Tyr Lys		
	340 345	350

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Leu Thr Gly Ala Val Met His Tyr Gly Asn Met Lys Phe Lys Gln Lys
 355 360 365

Gln Arg Glu Glu Gln Ala Glu Pro Asp Gly Thr Glu Val Ala Asp Lys
 370 375 380

Thr Ala Tyr Leu Met Gly Leu Asn Ser Ser Asp Leu Leu Lys Ala Leu
 385 390 395 400

Cys Phe Pro Arg Val Lys Val Gly Asn Glu Tyr Val Thr Lys Gly Gln
 405 410 415

Thr Val Asp Gln Val His His Ala Val Asn Ala Leu Ser Lys Ser Val
 420 425 430

Tyr Glu Lys Leu Phe Leu Trp Met Val Thr Arg Ile Asn Gln Gln Leu
 435 440 445

Asp Thr Lys Leu Pro Arg Gln His Phe Ile Gly Val Leu Asp Ile Ala
 450 455 460

Gly Phe Glu Ile Phe Glu Tyr Asn Ser Leu Glu Gln Leu Cys Ile Asn
 465 470 475 480

Phe Thr Asn Glu Lys Leu Gln Gln Phe Phe Asn His His Met Phe Val
 485 490 495

Leu Glu Gln Glu Glu Tyr Lys Lys Glu Gly Ile Glu Trp Thr Phe Ile
 500 505 510

Asp Phe Gly Met Asp Leu Ala Ala Cys Ile Glu Leu Ile Glu Lys Pro
 515 520 525

Met Gly Ile Phe Ser Ile Leu Glu Glu Glu Cys Met Phe Pro Lys Ala
 530 535 540

Thr Asp Thr Ser Phe Lys Asn Lys Leu Tyr Asp Gln His Leu Gly Lys
 545 550 555 560

Ser Asn Asn Phe Gln Lys Pro Lys Val Val Lys Gly Arg Ala Glu Ala
 565 570 575

His Phe Ser Leu Ile His Tyr Ala Gly Thr Val Asp Tyr Ser Val Ser
 580 585 590

- 134 -

Gly Trp Leu Glu Lys Asn Lys Asp Pro Leu Asn Glu Thr Val Val Gly
 595 600 605

Leu Tyr Gln Lys Ser Ser Asn Arg Leu Leu Ala His Leu Tyr Ala Thr
 610 615 620

Phe Ala Thr Ala Asp Ala Asp Ser Gly Lys Lys Lys Val Ala Lys Lys
 625 630 635 640

Lys Gly Ser Ser Phe Gln Thr Val Ser Ala Leu Phe Arg Glu Asn Leu
 645 650 655

Asn Lys Leu Met Ser Asn Leu Arg Thr Thr His Pro His Phe Val Arg
 660 665 670

Cys Ile Ile Pro Asn Glu Thr Lys Thr Pro Gly Ala Met Glu His Ser
 675 680 685

Leu Val Leu His Gln Leu Arg Cys Asn Gly Val Leu Glu Gly Ile Arg
 690 695 700

Ile Cys Arg Lys Gly Phe Pro Asn Arg Ile Leu Tyr Gly Asp Phe Lys
 705 710 715 720

Gln Arg Tyr Arg Val Leu Asn Ala Ser Ala Ile Leu Glu Gly Gln Phe
 725 730 735

Ile Asp Ser Lys Lys Ala Cys Glu Lys Leu Leu Ala Ser Ile Asp Ile
 740 745 750

Asp His Thr Gln Tyr Lys Phe Gly His Thr Lys Val Phe Phe Lys Ala
 755 760 765

Gly Leu Leu Gly Thr Leu Glu Glu Met Arg Asp Asp Arg Leu Ala Lys
 770 775 780

Leu Ile Thr Arg Thr Gln Ala Val Cys Arg Gly Phe Leu Met Arg Val
 785 790 795 800

Glu Phe Gln Lys Met Val Gln Arg Arg Glu Ser Ile Phe Cys Ile Gln
 805 810 815

Tyr Asn Ile Arg Ser Phe Met Asn Val Lys His Trp Pro Trp Met Lys
 820 825 830

- 135 -

Leu Phe Phe Lys Ile Lys Pro Leu Leu Lys Ser Ala Glu Thr Glu Lys
 835 840 845

Glu Met Ala Thr Met Lys Glu Glu Phe Gln Lys Thr Lys Asp Glu Leu
 850 855 860

Ala Lys Ser Glu Ala Lys Arg Lys Glu Leu Glu Glu Lys Leu Val Thr
 865 870 875 880

Leu Val Gln Glu Lys Asn Asp Leu Gln Leu Gln Val Gln Ala Glu Ser
 885 890 895

Glu Asn Leu Leu Asp Ala Glu Glu Arg Cys Asp Gln Leu Ile Lys Ala
 900 905 910

Lys Phe Gln Leu Glu Ala Lys Ile Lys Glu Val Thr Glu Arg Ala Glu
 915 920 925

Asp Glu Glu Glu Ile Asn Ala Glu Leu Thr Ala Lys Lys Arg Lys Leu
 930 935 940

Glu Asp Glu Cys Ser Glu Leu Lys Lys Asp Ile Asp Asp Leu Glu Leu
 945 950 955 960

Thr Leu Ala Lys Val Glu Lys Glu Lys His Ala Thr Glu Asn Lys Val
 965 970 975

Lys Asn Leu Thr Glu Glu Leu Ser Gly Leu Asp Glu Thr Ile Ala Lys
 980 985 990

Leu Thr Arg Glu Lys Lys Ala Leu Gln Glu Ala His Gln Gln Ala Leu
 995 1000 1005

Asp Asp Leu Gln Ala Glu Glu Asp Lys Val Asn Ser Leu Asn Lys
 1010 1015 1020

Thr Lys Ser Lys Leu Glu Gln Gln Val Glu Asp Leu Glu Ser Ser
 1025 1030 1035

Leu Glu Gln Glu Lys Lys Leu Arg Val Asp Leu Glu Arg Asn Lys
 1040 1045 1050

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Arg Lys	Leu Glu Gly Asp	Leu	Lys Leu Ala Gln	Glu	Ser Ile Leu
1055		1060		1065	
Asp Leu	Glu Asn Asp Lys	Gln	Gln Leu Asp Glu	Arg	Leu Lys Lys
1070		1075		1080	
Lys Asp	Phe Glu Tyr Cys	Gln	Leu Gln Ser Lys	Val	Glu Asp Glu
1085		1090		1095	
Gln Thr	Leu Gly Leu Gln	Phe	Gln Lys Lys Ile	Lys	Glu Leu Gln
1100		1105		1110	
Ala Arg	Ile Glu Glu Leu	Glu	Glu Glu Ile Glu	Ala	Glu Arg Ala
1115		1120		1125	
Thr Arg	Ala Lys Thr Glu	Lys	Gln Arg Ser Asp	Tyr	Ala Arg Glu
1130		1135		1140	
Leu Glu	Glu Leu Ser Glu	Arg	Leu Glu Glu Ala	Gly	Gly Val Thr
1145		1150		1155	
Ser Thr	Gln Ile Glu Leu	Asn	Lys Lys Arg Glu	Ala	Glu Phe Leu
1160		1165		1170	
Lys Leu	Arg Arg Asp Leu	Glu	Glu Ala Thr Leu	Gln	His Glu Ala
1175		1180		1185	
Met Val	Ala Thr Leu Arg	Lys	Lys His Ala Asp	Ser	Val Ala Glu
1190		1195		1200	
Leu Gly	Glu Gln Ile Asp	Asn	Leu Gln Arg Val	Lys	Gln Lys Leu
1205		1210		1215	
Glu Lys	Glu Lys Ser Glu	Phe	Lys Leu Glu Ile	Asp	Asp Leu Ser
1220		1225		1230	
Ser Ser	Met Glu Ser Val	Ser	Lys Ser Lys Ala	Asn	Leu Glu Lys
1235		1240		1245	
Ile Cys	Arg Thr Leu Glu	Asp	Gln Leu Ser Glu	Ala	Arg Gly Lys
1250		1255		1260	
Asn Glu	Glu Ile Gln Arg	Ser	Leu Ser Glu Leu	Thr	Thr Gln Lys
1265		1270		1275	

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Ser Arg Leu Gln Thr Glu Ala Gly Glu Leu Ser Arg Gln Leu Glu
1280 1285 1290

Glu Lys Glu Ser Ile Val Ser Gln Leu Ser Arg Ser Lys Gln Ala
1295 1300 1305

Phe Thr Gln Gln Thr Glu Glu Leu Lys Arg Gln Leu Glu Glu Glu
1310 1315 1320

Asn Lys Ala Lys Asn Ala Leu Ala His Ala Leu Gln Ser Ser Arg
1325 1330 1335

His Asp Cys Asp Leu Leu Arg Glu Gln Tyr Glu Glu Glu Gln Glu
1340 1345 1350

Gly Lys Ala Glu Leu Gln Arg Ala Leu Ser Lys Ala Asn Ser Glu
1355 1360 1365

Val Ala Gln Trp Arg Thr Lys Tyr Glu Thr Asp Ala Ile Gln Arg
1370 1375 1380

Thr Glu Glu Leu Glu Glu Ala Gln Glu Lys Leu Ala Gln Arg Leu
1385 1390 1395

Gln Asp Ser Glu Glu Gln Val Glu Ala Val Asn Ala Lys Cys Ala
1400 1405 1410

'Ser Leu Glu Lys Thr Lys Gln Arg Leu Gln Gly Glu Val Glu Asp
1415 1420 1425

Leu Met Val Asp Val Glu Arg Ala Asn Ser Leu Ala Ala Ala Leu
1430 1435 1440

Asp Lys Lys Gln Arg Asn Phe Asp Lys Val Leu Ala Glu Trp Lys
1445 1450 1455

Thr Lys Cys Glu Glu Ser Gln Ala Glu Leu Glu Ala Ser Leu Lys
1460 1465 1470

Glu Ser Arg Ser Leu Ser Thr Glu Leu Phe Lys Leu Lys Asn Ala
1475 1480 1485

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Tyr	Glu	Glu	Ala	Leu	Asp	Gln	Leu	Glu	Thr	Val	Lys	Arg	Glu	Asn
1490						1495					1500			
Lys	Asn	Leu	Glu	Gln	Glu	Ile	Ala	Asp	Leu	Thr	Glu	Gln	Ile	Ala
1505						1510					1515			
Glu	Asn	Gly	Lys	Thr	Ile	His	Glu	Leu	Glu	Lys	Ser	Arg	Lys	Gln
1520						1525					1530			
Ile	Glu	Leu	Glu	Lys	Ala	Asp	Ile	Gln	Leu	Ala	Leu	Glu	Glu	Ala
1535						1540					1545			
Glu	Ala	Ala	Leu	Glu	His	Glu	Glu	Ala	Lys	Ile	Leu	Arg	Ile	Gln
1550						1555					1560			
Leu	Glu	Leu	Thr	Gln	Val	Lys	Ser	Glu	Ile	Asp	Arg	Lys	Ile	Ala
1565						1570					1575			
Glu	Lys	Asp	Glu	Glu	Ile	Glu	Gln	Leu	Lys	Arg	Asn	Tyr	Gln	Arg
1580						1585					1590			
Thr	Val	Glu	Thr	Met	Gln	Ser	Ala	Leu	Asp	Ala	Glu	Val	Arg	Ser
1595						1600					1605			
Arg	Asn	Glu	Ala	Ile	Arg	Leu	Lys	Lys	Lys	Met	Glu	Gly	Asp	Leu
1610						1615					1620			
Asn	Glu	Ile	Glu	Ile	Gln	Leu	Ser	His	Ala	Asn	Arg	Gln	Ala	Ala
1625						1630					1635			
Glu	Thr	Leu	Lys	His	Leu	Arg	Ser	Val	Gln	Gly	Gln	Leu	Lys	Asp
1640						1645					1650			
Thr	Gln	Leu	His	Leu	Asp	Asp	Ala	Leu	Arg	Gly	Gln	Glu	Asp	Leu
1655						1660					1665			
Lys	Glu	Gln	Leu	Ala	Ile	Val	Glu	Arg	Arg	Ala	Asn	Leu	Leu	Gln
1670						1675					1680			
Ala	Glu	Val	Glu	Glu	Leu	Arg	Ala	Thr	Leu	Glu	Gln	Thr	Glu	Arg
1685						1690					1695			
Ala	Arg	Lys	Leu	Ala	Glu	Gln	Glu	Leu	Leu	Asp	Ser	Asn	Glu	Arg
1700						1705					1710			

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Val Gln Leu Leu His Thr Gln Asn Thr Ser Leu Ile His Thr Lys
1715 1720 1725

Lys Lys Leu Glu Thr Asp Leu Met Gln Leu Gln Ser Glu Val Glu
1730 1735 1740

Asp Ala Ser Arg Asp Ala Arg Asn Ala Glu Glu Lys Ala Lys Lys
1745 1750 1755

Ala Ile Thr Asp Ala Ala Met Met Ala Glu Glu Leu Lys Lys Glu
1760 1765 1770

Gln Asp Thr Ser Ala His Leu Glu Arg Met Lys Lys Asn Leu Glu
1775 1780 1785

Gln Thr Val Lys Asp Leu Gln His Arg Leu Asp Glu Ala Glu Gln
1790 1795 1800

Leu Ala Leu Lys Gly Gly Lys Lys Gln Ile Gln Lys Leu Glu Thr
1805 1810 1815

Arg Ile Arg Glu Leu Glu Phe Glu Leu Glu Gly Glu Gln Lys Lys
1820 1825 1830

Asn Thr Glu Ser Val Lys Gly Leu Arg Lys Tyr Glu Arg Arg Val
1835 1840 1845

Lys Glu Leu Thr Tyr Gln Ser Glu Glu Asp Arg Lys Asn Val Leu
1850 1855 1860

Arg Leu Gln Asp Leu Val Asp Lys Leu Gln Val Lys Val Lys Ser
1865 1870 1875

Tyr Lys Arg Gln Ala Glu Glu Ala Asp Glu Gln Ala Asn Ala His
1880 1885 1890

Leu Thr Lys Phe Arg Lys Ala Gln His Glu Leu Glu Glu Ala Glu
1895 1900 1905

Glu Arg Ala Asp Ile Ala Glu Ser Gln Val Asn Lys Leu Arg Ala
1910 1915 1920

Lys Thr Arg Asp Phe Thr Ser Ser Arg Met Val Val His Glu Ser
1925 1930 1935

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Glu Glu
1940

<210> 81

<211> 943

<212> PRT

<213> Homo sapiens

<400> 81

Met Thr Gln Arg Ser Ile Ala Gly Pro Ile Cys Asn Leu Lys Phe Val
1 5 10 15

Thr Leu Leu Val Ala Leu Ser Ser Glu Leu Pro Phe Leu Gly Ala Gly
20 25 30

Val Gln Leu Gln Asp Asn Gly Tyr Asn Gly Leu Leu Ile Ala Ile Asn
35 40 45

Pro Gln Val Pro Glu Asn Gln Asn Leu Ile Ser Asn Ile Lys Glu Met
50 55 60

Ile Thr Glu Ala Ser Phe Tyr Leu Phe Asn Ala Thr Lys Arg Arg Val
65 70 75 80

Phe Phe Arg Asn Ile Lys Ile Leu Ile Pro Ala Thr Trp Lys Ala Asn
85 90 95

Asn Asn Ser Lys Ile Lys Gln Glu Ser Tyr Glu Lys Ala Asn Val Ile
100 105 110

Val Thr Asp Trp Tyr Gly Ala His Gly Asp Asp Pro Tyr Thr Leu Gln
115 120 125

Tyr Arg Gly Cys Gly Lys Glu Gly Lys Tyr Ile His Phe Thr Pro Asn
130 135 140

Phe Leu Leu Asn Asp Asn Leu Thr Ala Gly Tyr Gly Ser Arg Gly Arg
145 150 155 160

Val Phe Val His Glu Trp Ala His Leu Arg Trp Gly Val Phe Asp Glu

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	165		170		175														
Tyr	Ile	Asn	Asp	Lys	Pro	Phe	Tyr	Ile	Asn	Gly	Gln	Asn	Gln	Ile	Lys				
		180						185					190						
Val	Thr	Arg	Cys	Ser	Ser	Asp	Ile	Thr	Gly	Ile	Phe	Val	Cys	Glu	Lys				
		195					200					205							
Gly	Pro	Cys	Pro	Gln	Glu	Asn	Cys	Ile	Ile	Ser	Lys	Leu	Phe	Lys	Glu				
	210					215					220								
Gly	Cys	Thr	Phe	Ile	Tyr	Asn	Ser	Thr	Gln	Asn	Ala	Thr	Ala	Ser	Ile				
	225				230					235					240				
Met	Phe	Met	Gln	Ser	Leu	Ser	Ser	Val	Val	Glu	Phe	Cys	Asn	Ala	Ser				
			245						250					255					
Thr	His	Asn	Gln	Glu	Ala	Pro	Asn	Leu	Gln	Asn	Gln	Met	Cys	Ser	Leu				
		260						265					270						
Arg	Ser	Ala	Trp	Asp	Val	Ile	Thr	Asp	Ser	Ala	Asp	Phe	His	His	Ser				
		275					280					285							
Phe	Pro	Met	Asn	Gly	Thr	Glu	Leu	Pro	Pro	Pro	Pro	Thr	Phe	Ser	Leu				
	290					295					300								
Val	Gln	Ala	Gly	Asp	Lys	Val	Val	Cys	Leu	Val	Leu	Asp	Val	Ser	Ser				
	305				310					315					320				
Lys	Met	Ala	Glu	Ala	Asp	Arg	Leu	Leu	Gln	Leu	Gln	Gln	Ala	Ala	Glu				
			325						330					335					
Phe	Tyr	Leu	Met	Gln	Ile	Val	Glu	Ile	His	Thr	Phe	Val	Gly	Ile	Ala				
		340						345					350						
Ser	Phe	Asp	Ser	Lys	Gly	Glu	Ile	Arg	Ala	Gln	Leu	His	Gln	Ile	Asn				
		355					360					365							
Ser	Asn	Asp	Asp	Arg	Lys	Leu	Leu	Val	Ser	Tyr	Leu	Pro	Thr	Thr	Val				
	370					375					380								
Ser	Ala	Lys	Thr	Asp	Ile	Ser	Ile	Cys	Ser	Gly	Leu	Lys	Lys	Gly	Phe				
	385				390					395					400				

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Glu Val Val Glu Lys Leu Asn Gly Lys Ala Tyr Gly Ser Val Met Ile
 405 410 415

Leu Val Thr Ser Gly Asp Asp Lys Leu Leu Gly Asn Cys Leu Pro Thr
 420 425 430

Val Leu Ser Ser Gly Ser Thr Ile His Ser Ile Ala Leu Gly Ser Ser
 435 440 445

Ala Ala Pro Asn Leu Glu Glu Leu Ser Arg Leu Thr Gly Gly Leu Lys
 450 455 460

Phe Phe Val Pro Asp Ile Ser Asn Ser Asn Ser Met Ile Asp Ala Phe
 465 470 475 480

Ser Arg Ile Ser Ser Gly Thr Gly Asp Ile Phe Gln Gln His Ile Gln
 485 490 495

Leu Glu Ser Thr Gly Glu Asn Val Lys Pro His His Gln Leu Lys Asn
 500 505 510

Thr Val Thr Val Asp Asn Thr Val Gly Asn Asp Thr Met Phe Leu Val
 515 520 525

Thr Trp Gln Ala Ser Gly Pro Pro Glu Ile Ile Leu Phe Asp Pro Asp
 530 535 540

Gly Arg Lys Tyr Tyr Thr Asn Asn Phe Ile Thr Asn Leu Thr Phe Arg
 545 550 555 560

Thr Ala Ser Leu Trp Ile Pro Gly Thr Ala Lys Pro Gly His Trp Thr
 565 570 575

Tyr Thr Leu Asn Asn Thr His His Ser Leu Gln Ala Leu Lys Val Thr
 580 585 590

Val Thr Ser Arg Ala Ser Asn Ser Ala Val Pro Pro Ala Thr Val Glu
 595 600 605

Ala Phe Val Glu Arg Asp Ser Leu His Phe Pro His Pro Val Met Ile
 610 615 620

Tyr Ala Asn Val Lys Gln Gly Phe Tyr Pro Ile Leu Asn Ala Thr Val
 625 630 635 640

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Thr Ala Thr Val Glu Pro Glu Thr Gly Asp Pro Val Thr Leu Arg Leu
645 650 655

Leu Asp Asp Gly Ala Gly Ala Asp Val Ile Lys Asn Asp Gly Ile Tyr
660 665 670

Ser Arg Tyr Phe Phe Ser Phe Ala Ala Asn Gly Arg Tyr Ser Leu Lys
675 680 685

Val His Val Asn His Ser Pro Ser Ile Ser Thr Pro Ala His Ser Ile
690 695 700

Pro Gly Ser His Ala Met Tyr Val Pro Gly Tyr Thr Ala Asn Gly Asn
705 710 715 720

Ile Gln Met Asn Ala Pro Arg Lys Ser Val Gly Arg Asn Glu Glu Glu
725 730 735

Arg Lys Trp Gly Phe Ser Arg Val Ser Ser Gly Gly Ser Phe Ser Val
740 745 750

Leu Gly Val Pro Ala Gly Pro His Pro Asp Val Phe Pro Pro Cys Lys
755 760 765

Ile Ile Asp Leu Glu Ala Val Lys Val Glu Glu Glu Leu Thr Leu Ser
770 775 780

Trp Thr Ala Pro Gly Glu Asp Phe Asp Gln Gly Gln Ala Thr Ser Tyr
785 790 795 800

Glu Ile Arg Met Ser Lys Ser Leu Gln Asn Ile Gln Asp Asp Phe Asn
805 810 815

Asn Ala Ile Leu Val Asn Thr Ser Lys Arg Asn Pro Gln Gln Ala Gly
820 825 830

Ile Arg Glu Ile Phe Thr Phe Ser Pro Gln Ile Ser Thr Asn Gly Pro
835 840 845

Glu His Gln Pro Asn Gly Glu Thr His Glu Ser His Arg Ile Tyr Val
850 855 860

Ala Ile Arg Ala Met Asp Arg Asn Ser Leu Gln Ser Ala Val Ser Asn
865 870 875 880

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Ile Ala Gln Ala Pro Leu Phe Ile Pro Pro Asn Ser Asp Pro Val Pro
 885 890 895

Ala Arg Asp Tyr Leu Ile Leu Lys Gly Val Leu Thr Ala Met Gly Leu
 900 905 910

Ile Gly Ile Ile Cys Leu Ile Ile Val Val Thr His His Thr Leu Ser
 915 920 925

Arg Lys Lys Arg Ala Asp Lys Lys Glu Asn Gly Thr Lys Leu Leu
 930 935 940

<210> 82

<211> 294

<212> PRT

<213> Homo sapiens

<400> 82

Met Gln Pro Glu Gly Ala Glu Lys Gly Lys Ser Phe Lys Gln Arg Leu
 1 5 10 15

Val Leu Lys Ser Ser Leu Ala Lys Glu Thr Leu Ser Glu Phe Leu Gly
 20 25 30

Thr Phe Ile Leu Ile Val Leu Gly Cys Gly Cys Val Ala Gln Ala Ile
 35 40 45

Leu Ser Arg Gly Arg Phe Gly Gly Val Ile Thr Ile Asn Val Gly Phe
 50 55 60

Ser Met Ala Val Ala Met Ala Ile Tyr Val Ala Gly Gly Val Ser Gly
 65 70 75 80

Gly His Ile Asn Pro Ala Val Ser Leu Ala Met Cys Leu Phe Gly Arg
 85 90 95

Met Lys Trp Phe Lys Leu Pro Phe Tyr Val Gly Ala Gln Phe Leu Gly
 100 105 110

Ala Phe Val Gly Ala Ala Thr Val Phe Gly Ile Tyr Tyr Asp Gly Leu

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115 120 125
 Met Ser Phe Ala Gly Gly Lys Leu Leu Ile Val Gly Glu Asn Ala Thr
 130 135 140
 Ala His Ile Phe Ala Thr Tyr Pro Ala Pro Tyr Leu Ser Leu Ala Asn
 145 150 155 160
 Ala Phe Ala Asp Gln Val Val Ala Thr Met Ile Leu Leu Ile Ile Val
 165 170 175
 Phe Ala Ile Phe Asp Ser Arg Asn Leu Gly Ala Pro Arg Gly Leu Glu
 180 185 190
 Pro Ile Ala Ile Gly Leu Leu Ile Ile Val Ile Ala Ser Ser Leu Gly
 195 200 205
 Leu Asn Ser Gly Cys Ala Met Asn Pro Ala Arg Asp Leu Ser Pro Arg
 210 215 220
 Leu Phe Thr Ala Leu Ala Gly Trp Gly Phe Glu Val Phe Arg Ala Gly
 225 230 235 240
 Asn Asn Phe Trp Trp Ile Pro Val Val Gly Pro Leu Val Gly Ala Val
 245 250 255
 Ile Gly Gly Leu Ile Tyr Val Leu Val Ile Glu Ile His His Pro Glu
 260 265 270
 Pro Asp Ser Val Phe Lys Ala Glu Gln Ser Glu Asp Lys Pro Glu Lys
 275 280 285
 Tyr Glu Leu Ser Val Ile
 290

<210> 83

<211> 292

<212> PRT

<213> Homo sapiens

<400> 83

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Met Gly Arg Gln Lys Glu Leu Val Ser Arg Cys Gly Glu Met Leu His
 1 5 10 15

Ile Arg Tyr Arg Leu Leu Arg Gln Ala Leu Ala Glu Cys Leu Gly Thr
 20 25 30

Leu Ile Leu Val Met Phe Gly Cys Gly Ser Val Ala Gln Val Val Leu
 35 40 45

Ser Arg Gly Thr His Gly Gly Phe Leu Thr Ile Asn Leu Ala Phe Gly
 50 55 60

Phe Ala Val Thr Leu Gly Ile Leu Ile Ala Gly Gln Val Ser Gly Ala
 65 70 75 80

His Leu Asn Pro Ala Val Thr Phe Ala Met Cys Phe Leu Ala Arg Glu
 85 90 95

Pro Trp Ile Lys Leu Pro Ile Tyr Thr Leu Ala Gln Thr Leu Gly Ala
 100 105 110

Phe Leu Gly Ala Gly Ile Val Phe Gly Leu Tyr Tyr Asp Ala Ile Trp
 115 120 125

His Phe Ala Asp Asn Gln Leu Phe Val Ser Gly Pro Asn Gly Thr Ala
 130 135 140

Gly Ile Phe Ala Thr Tyr Pro Ser Gly His Leu Asp Met Ile Asn Gly
 145 150 155 160

Phe Phe Asp Gln Phe Ile Gly Thr Ala Ser Leu Ile Val Cys Val Leu
 165 170 175

Ala Ile Val Asp Pro Tyr Asn Asn Pro Val Pro Arg Gly Leu Glu Ala
 180 185 190

Phe Thr Val Gly Leu Val Val Leu Val Ile Gly Thr Ser Met Gly Phe
 195 200 205

Asn Ser Gly Tyr Ala Val Asn Pro Ala Arg Asp Phe Gly Pro Arg Leu
 210 215 220

Phe Thr Ala Leu Ala Gly Trp Gly Ser Ala Val Phe Thr Thr Gly Gln
 225 230 235 240

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His Trp Trp Trp Val Pro Ile Val Ser Pro Leu Leu Gly Ser Ile Ala
 245 250 255

Gly Val Phe Val Tyr Gln Leu Met Ile Gly Cys His Leu Glu Gln Pro
 260 265 270

Pro Pro Ser Asn Glu Glu Glu Asn Val Lys Leu Ala His Val Lys His
 275 280 285

Lys Glu Gln Ile
 290

<210> 84

<211> 283

<212> PRT

<213> Homo sapiens

<400> 84

Met Ala Val Pro Pro Thr Tyr Ala Asp Leu Gly Lys Ser Ala Arg Asp
 1 5 10 15

Val Phe Thr Lys Gly Tyr Gly Phe Gly Leu Ile Lys Leu Asp Leu Lys
 20 25 30

Thr Lys Ser Glu Asn Gly Leu Glu Phe Thr Ser Ser Gly Ser Ala Asn
 35 40 45

Thr Glu Thr Thr Lys Val Thr Gly Ser Leu Glu Thr Lys Tyr Arg Trp
 50 55 60

Thr Glu Tyr Gly Leu Thr Phe Thr Glu Lys Trp Asn Thr Asp Asn Thr
 65 70 75 80

Leu Gly Thr Glu Ile Thr Val Glu Asp Gln Leu Ala Arg Gly Leu Lys
 85 90 95

Leu Thr Phe Asp Ser Ser Phe Ser Pro Asn Thr Gly Lys Lys Asn Ala
 100 105 110

Lys Ile Lys Thr Gly Tyr Lys Arg Glu His Ile Asn Leu Gly Cys Asp
 115 120 125

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Met Asp Phe Asp Ile Ala Gly Pro Ser Ile Arg Gly Ala Leu Val Leu
 130 135 140

Gly Tyr Glu Gly Trp Leu Ala Gly Tyr Gln Met Asn Phe Glu Thr Ala
 145 150 155 160

Lys Ser Arg Val Thr Gln Ser Asn Phe Ala Val Gly Tyr Lys Thr Asp
 165 170 175

Glu Phe Gln Leu His Thr Asn Val Asn Asp Gly Thr Glu Phe Gly Gly
 180 185 190

Ser Ile Tyr Gln Lys Val Asn Lys Lys Leu Glu Thr Ala Val Asn Leu
 195 200 205

Ala Trp Thr Ala Gly Asn Ser Asn Thr Arg Phe Gly Ile Ala Ala Lys
 210 215 220

Tyr Gln Ile Asp Pro Asp Ala Cys Phe Ser Ala Lys Val Asn Asn Ser
 225 230 235 240

Ser Leu Ile Gly Leu Gly Tyr Thr Gln Thr Leu Lys Pro Gly Ile Lys
 245 250 255

Leu Thr Leu Ser Ala Leu Leu Asp Gly Lys Asn Val Asn Ala Gly Gly
 260 265 270

His Lys Leu Gly Leu Gly Leu Glu Phe Gln Ala
 275 280

<210> 85

<211> 195

<212> PRT

<213> Homo sapiens

<400> 85

Met Gly Ser Arg Ala Ser Thr Leu Leu Arg Asp Glu Glu Leu Glu Glu
 1 5 10 15

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Ile Lys Lys Glu Thr Gly Phe Ser His Ser Gln Ile Thr Arg Leu Tyr
 20 25 30

Ser Arg Phe Thr Ser Leu Asp Lys Gly Glu Asn Gly Thr Leu Ser Arg
 35 40 45

Glu Asp Phe Gln Arg Ile Pro Glu Leu Ala Ile Asn Pro Leu Gly Asp
 50 55 60

Arg Ile Ile Asn Ala Phe Phe Pro Glu Gly Glu Asp Gln Val Asn Phe
 65 70 75 80

Arg Gly Phe Met Arg Thr Leu Ala His Phe Arg Pro Ile Glu Asp Asn
 85 90 95

Glu Lys^{*} Ser Lys Asp Val Asn Gly Pro Glu Pro Leu Asn Ser Arg Ser
 100 105 110

Asn Lys Leu His Phe Ala Phe Arg Leu Tyr Asp Leu Asp Lys Asp Glu
 115 120 125

Lys Ile Ser Arg Asp Glu Leu Leu Gln Val Leu Arg Met Met Val Gly
 130 135 140

Val Asn Ile Ser Asp Glu Gln Leu Gly Ser Ile Ala Asp Arg Thr Ile
 145 150 155 160

Gln Glu Ala Asp Gln Asp Gly Asp Ser Ala Ile Ser Phe Thr Glu Phe
 165 170 175

Val Lys Val Leu Glu Lys Val Asp Val Glu Gln Lys Met Ser Ile Arg
 180 185 190

Phe Leu His
 195

<210> 86

<211> 535

<212> PRT

<213> Homo sapiens

<400> 86

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Met Ala Ser Leu Ser Leu Ala Pro Val Asn Ile Phe Lys Ala Gly Ala
 1 5 10 15
 Asp Glu Glu Arg Ala Glu Thr Ala Arg Leu Thr Ser Phe Ile Gly Ala
 20 25 30
 Ile Ala Ile Gly Asp Leu Val Lys Ser Thr Leu Gly Pro Lys Gly Met
 35 40 45
 Asp Lys Ile Leu Leu Ser Ser Gly Arg Asp Ala Ser Leu Met Val Thr
 50 55 60
 Asn Asp Gly Ala Thr Ile Leu Lys Asn Ile Gly Val Asp Asn Pro Ala
 65 70 75 80
 Ala Lys Val Leu Val Asp Met Ser Arg Val Gln Asp Asp Glu Val Gly
 85 90 95
 Asp Gly Thr Thr Ser Val Thr Val Leu Ala Ala Glu Leu Leu Arg Glu
 100 105 110
 Ala Glu Ser Leu Ile Ala Lys Lys Ile His Pro Gln Thr Ile Ile Ala
 115 120 125
 Gly Trp Arg Glu Ala Thr Lys Ala Ala Arg Glu Ala Leu Leu Ser Ser
 130 135 140
 Ala Val Asp His Gly Ser Asp Glu Val Lys Phe Arg Gln Asp Leu Met
 145 150 155 160
 Asn Ile Ala Gly Thr Thr Leu Ser Ser Lys Leu Leu Thr His His Lys
 165 170 175
 Asp His Phe Thr Lys Leu Ala Val Glu Ala Val Leu Arg Leu Lys Gly
 180 185 190
 Ser Gly Asn Leu Glu Ala Ile His Ile Ile Lys Lys Leu Gly Gly Ser
 195 200 205
 Leu Ala Asp Ser Tyr Leu Asp Glu Gly Phe Leu Leu Asp Lys Lys Ile
 210 215 220
 Gly Val Asn Gln Pro Lys Arg Ile Glu Asn Ala Lys Ile Leu Ile Ala
 225 230 235 240

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Asn Thr Gly Met Asp Thr Asp Lys Ile Lys Ile Phe Gly Ser Arg Val
 245 250 255

Arg Val Asp Ser Thr Ala Lys Val Ala Glu Ile Glu His Ala Glu Lys
 260 265 270

Glu Lys Met Lys Glu Lys Val Glu Arg Ile Leu Lys His Gly Ile Asn
 275 280 285

Cys Phe Ile Asn Arg Gln Leu Ile Tyr Asn Tyr Pro Glu Gln Leu Phe
 290 295 300

Gly Ala Ala Gly Val Met Ala Ile Glu His Ala Asp Phe Ala Gly Val
 305 310 315 320

Glu Arg Leu Ala Leu Val Thr Gly Gly Glu Ile Ala Ser Thr Phe Asp
 325 330 335

His Pro Glu Leu Val Lys Leu Gly Ser Cys Lys Leu Ile Glu Glu Val
 340 345 350

Met Ile Gly Glu Asp Lys Leu Ile His Phe Ser Gly Val Ala Leu Gly
 355 360 365

Glu Ala Cys Thr Ile Val Leu Arg Gly Ala Thr Gln Gln Ile Leu Asp
 370 375 380

Glu Ala Glu Arg Ser Leu His Asp Ala Leu Cys Val Leu Ala Gln Thr
 385 390 395 400

Val Lys Asp Ser Arg Thr Val Tyr Gly Gly Gly Cys Ser Glu Met Leu
 405 410 415

Met Ala His Ala Val Thr Gln Leu Ala Asn Arg Thr Pro Gly Lys Glu
 420 425 430

Ala Val Ala Met Glu Ser Tyr Ala Lys Ala Leu Arg Met Leu Pro Thr
 435 440 445

Ile Ile Ala Asp Asn Ala Gly Tyr Asp Ser Ala Asp Leu Val Ala Gln
 450 455 460

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Leu Arg Ala Ala His Ser Glu Gly Asn Thr Thr Ala Gly Leu Asp Met
 465 470 475 480

Arg Glu Gly Thr Ile Gly Asp Met Ala Ile Leu Gly Ile Thr Glu Ser
 485 490 495

Phe Gln Val Lys Arg Gln Val Leu Leu Ser Ala Ala Glu Ala Ala Glu
 500 505 510

Val Ile Leu Arg Val Asp Asn Ile Ile Lys Ala Ala Pro Arg Lys Arg
 515 520 525

Val Pro Asp His His Pro Cys
 530 535

<210> 87

<211> 447

<212> PRT

<213> Homo sapiens

<400> 87

Met Ser Leu Trp Leu Gly Ala Pro Val Pro Asp Ile Pro Pro Asp Ser
 1 5 10 15

Ala Val Glu Leu Trp Lys Pro Gly Ala Gln Asp Ala Ser Ser Gln Ala
 20 25 30

Gln Gly Gly Ser Ser Cys Ile Leu Arg Glu Glu Ala Arg Met Pro His
 35 40 45

Ser Ala Gly Gly Thr Ala Gly Val Gly Leu Glu Ala Ala Glu Pro Thr
 50 55 60

Ala Leu Leu Thr Arg Ala Glu Pro Pro Ser Glu Pro Thr Glu Ile Arg
 65 70 75 80

Pro Gln Lys Arg Lys Lys Gly Pro Ala Pro Lys Met Leu Gly Asn Glu
 85 90 95

Leu Cys Ser Val Cys Gly Asp Lys Ala Ser Gly Phe His Tyr Asn Val
 100 105 110

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Leu Ser Cys Glu Gly Cys Lys Gly Phe Phe Arg Arg Ser Val Ile Lys
 115 120 125

Gly Ala His Tyr Ile Cys His Ser Gly Gly His Cys Pro Met Asp Thr
 130 135 140

Tyr Met Arg Arg Lys Cys Gln Glu Cys Arg Leu Arg Lys Cys Arg Gln
 145 150 155 160

Ala Gly Met Arg Glu Glu Cys Val Leu Ser Glu Glu Gln Ile Arg Leu
 165 170 175

Lys Lys Leu Lys Arg Gln Glu Glu Glu Gln Ala His Ala Thr Ser Leu
 180 185 190

Pro Pro Arg Arg Ser Ser Pro Pro Gln Ile Leu Pro Gln Leu Ser Pro
 195 200 205

Glu Gln Leu Gly Met Ile Glu Lys Leu Val Ala Ala Gln Gln Gln Cys
 210 215 220

Asn Arg Arg Ser Phe Ser Asp Arg Leu Arg Val Thr Pro Trp Pro Met
 225 230 235 240

Ala Pro Asp Pro His Ser Arg Glu Ala Arg Gln Gln Arg Phe Ala His
 245 250 255

Phe Thr Glu Leu Ala Ile Val Ser Val Gln Glu Ile Val Asp Phe Ala
 260 265 270

Lys Gln Leu Pro Gly Phe Leu Gln Leu Ser Arg Glu Asp Gln Ile Ala
 275 280 285

Leu Leu Lys Thr Ser Ala Ile Glu Val Met Leu Leu Glu Thr Ser Arg
 290 295 300

Arg Tyr Asn Pro Gly Ser Glu Ser Ile Thr Phe Leu Lys Asp Phe Ser
 305 310 315 320

Tyr Asn Arg Glu Asp Phe Ala Lys Ala Gly Leu Gln Val Glu Phe Ile
 325 330 335

Asn Pro Ile Phe Glu Phe Ser Arg Ala Met Asn Glu Leu Gln Leu Asn
 340 345 350

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Asp Ala Glu Phe Ala Leu Leu Ile Ala Ile Ser Ile Phe Ser Ala Asp
 355 360 365

Arg Pro Asn Val Gln Asp Gln Leu Gln Val Glu Arg Leu Gln His Thr
 370 375 380

Tyr Val Glu Ala Leu His Ala Tyr Val Ser Ile His His Pro His Asp
 385 390 395 400

Arg Leu Met Phe Pro Arg Met Leu Met Lys Leu Val Ser Leu Arg Thr
 405 410 415

Leu Ser Ser Val His Ser Glu Gln Val Phe Ala Leu Arg Leu Gln Asp
 420 425 430

Lys Lys Leu Pro Pro Leu Leu Ser Glu Ile Trp Asp Val His Glu
 435 440 445

<210> 88

<211> 826

<212> PRT

<213> Homo sapiens

<400> 88

Met Glu Gly Ala Gly Gly Ala Asn Asp Lys Lys Lys Ile Ser Ser Glu
 1 5 10 15

Arg Arg Lys Glu Lys Ser Arg Asp Ala Ala Arg Ser Arg Arg Ser Lys
 20 25 30

Glu Ser Glu Val Phe Tyr Glu Leu Ala His Gln Leu Pro Leu Pro His
 35 40 45

Asn Val Ser Ser His Leu Asp Lys Ala Ser Val Met Arg Leu Thr Ile
 50 55 60

Ser Tyr Leu Arg Val Arg Lys Leu Leu Asp Ala Gly Asp Leu Asp Ile
 65 70 75 80

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Glu Asp Asp Met Lys Ala Gln Met Asn Cys Phe Tyr Leu Lys Ala Leu
85 90 95

Asp Gly Phe Val Met Val Leu Thr Asp Asp Gly Asp Met Ile Tyr Ile
100 105 110

Ser Asp Asn Val Asn Lys Tyr Met Gly Leu Thr Gln Phe Glu Leu Thr
115 120 125

Gly His Ser Val Phe Asp Phe Thr His Pro Cys Asp His Glu Glu Met
130 135 140

Arg Glu Met Leu Thr His Arg Asn Gly Leu Val Lys Lys Gly Lys Glu
145 150 155 160

Gln Asn Thr Gln Arg Ser Phe Phe Leu Arg Met Lys Cys Thr Leu Thr
165 170 175

Ser Arg Gly Arg Thr Met Asn Ile Lys Ser Ala Thr Trp Lys Val Leu
180 185 190

His Cys Thr Gly His Ile His Val Tyr Asp Thr Asn Ser Asn Gln Pro
195 200 205

Gln Cys Gly Tyr Lys Lys Pro Pro Met Thr Cys Leu Val Leu Ile Cys
210 215 220

Glu Pro Ile Pro His Pro Ser Asn Ile Glu Ile Pro Leu Asp Ser Lys
225 230 235 240

Thr Phe Leu Ser Arg His Ser Leu Asp Met Lys Phe Ser Tyr Cys Asp
245 250 255

Glu Arg Ile Thr Glu Leu Met Gly Tyr Glu Pro Glu Glu Leu Leu Gly
260 265 270

Arg Ser Ile Tyr Glu Tyr Tyr His Ala Leu Asp Ser Asp His Leu Thr
275 280 285

Lys Thr His His Asp Met Phe Thr Lys Gly Gln Val Thr Thr Gly Gln
290 295 300

Tyr Arg Met Leu Ala Lys Arg Gly Gly Tyr Val Trp Val Glu Thr Gln
305 310 315 320

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Ala Thr Val Ile Tyr Asn Thr Lys Asn Ser Gln Pro Gln Cys Ile Val
 325 330 335

Cys Val Asn Tyr Val Val Ser Gly Ile Ile Gln His Asp Leu Ile Phe
 340 345 350

Ser Leu Gln Gln Thr Glu Cys Val Leu Lys Pro Val Glu Ser Ser Asp
 355 360 365

Met Lys Met Thr Gln Leu Phe Thr Lys Val Glu Ser Glu Asp Thr Ser
 370 375 380

Ser Leu Phe Asp Lys Leu Lys Lys Glu Pro Asp Ala Leu Thr Leu Leu
 385 390 395 400

Ala Pro Ala Ala Gly Asp Thr Ile Ile Ser Leu Asp Phe Gly Ser Asn
 405 410 415

Asp Thr Glu Thr Asp Asp Gln Gln Leu Glu Glu Val Pro Leu Tyr Asn
 420 425 430

Asp Val Met Leu Pro Ser Pro Asn Glu Lys Leu Gln Asn Ile Asn Leu
 435 440 445

Ala Met Ser Pro Leu Pro Thr Ala Glu Thr Pro Lys Pro Leu Arg Ser
 450 455 460

Ser Ala Asp Pro Ala Leu Asn Gln Glu Val Ala Leu Lys Leu Glu Pro
 465 470 475 480

Asn Pro Glu Ser Leu Glu Leu Ser Phe Thr Met Pro Gln Ile Gln Asp
 485 490 495

Gln Thr Pro Ser Pro Ser Asp Gly Ser Thr Arg Gln Ser Ser Pro Glu
 500 505 510

Pro Asn Ser Pro Ser Glu Tyr Cys Phe Tyr Val Asp Ser Asp Met Val
 515 520 525

Asn Glu Phe Lys Leu Glu Leu Val Glu Lys Leu Phe Ala Glu Asp Thr
 530 535 540

Glu Ala Lys Asn Pro Phe Ser Thr Gln Asp Thr Asp Leu Asp Leu Glu
 545 550 555 560

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Met Leu Ala Pro Tyr Ile Pro Met Asp Asp Asp Phe Gln Leu Arg Ser
565 570 575

Phe Asp Gln Leu Ser Pro Leu Glu Ser Ser Ser Ala Ser Pro Glu Ser
580 585 590

Ala Ser Pro Gln Ser Thr Val Thr Val Phe Gln Gln Thr Gln Ile Gln
595 600 605

Glu Pro Thr Ala Asn Ala Thr Thr Thr Thr Ala Thr Thr Asp Glu Leu
610 615 620

Lys Thr Val Thr Lys Asp Arg Met Glu Asp Ile Lys Ile Leu Ile Ala
625 630 635 640

Ser Pro Ser Pro Thr His Ile His Lys Glu Thr Thr Ser Ala Thr Ser
645 650 655

Ser Pro Tyr Arg Asp Thr Gln Ser Arg Thr Ala Ser Pro Asn Arg Ala
660 665 670

Gly Lys Gly Val Ile Glu Gln Thr Glu Lys Ser His Pro Arg Ser Pro
675 680 685

Asn Val Leu Ser Val Ala Leu Ser Gln Arg Thr Thr Val Pro Glu Glu
690 695 700

Glu Leu Asn Pro Lys Ile Leu Ala Leu Gln Asn Ala Gln Arg Lys Arg
705 710 715 720

Lys Met Glu His Asp Gly Ser Leu Phe Gln Ala Val Gly Ile Gly Thr
725 730 735

Leu Leu Gln Gln Pro Asp Asp His Ala Ala Thr Thr Ser Leu Ser Trp
740 745 750

Lys Arg Val Lys Gly Cys Lys Ser Ser Glu Gln Asn Gly Met Glu Gln
755 760 765

Lys Thr Ile Ile Leu Ile Pro Ser Asp Leu Ala Cys Arg Leu Leu Gly
770 775 780

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Gln Ser Met Asp Glu Ser Gly Leu Pro Gln Leu Thr Ser Tyr Asp Cys
 785 790 795 800

Glu Val Asn Ala Pro Ile Gln Gly Ser Arg Asn Leu Leu Gln Gly Glu
 805 810 815

Glu Leu Leu Arg Ala Leu Asp Gln Val Asn
 820 825

<210> 89

<211> 1575

<212> PRT

<213> Homo sapiens

<400> 89

Met Pro His Glu Glu Leu Pro Ser Leu Gln Arg Pro Arg Tyr Gly Ser
 1 5 10 15

Ile Val Asp Asp Glu Arg Leu Ser Ala Glu Glu Met Asp Glu Arg Arg
 20 25 30

Arg Gln Asn Ile Ala Tyr Glu Tyr Leu Cys His Leu Glu Glu Ala Lys
 35 40 45

Arg Trp Met Glu Val Cys Leu Val Glu Glu Leu Pro Pro Thr Thr Glu
 50 55 60

Leu Glu Glu Gly Leu Arg Asn Gly Val Tyr Leu Ala Lys Leu Ala Lys
 65 70 75 80

Phe Phe Ala Pro Lys Met Val Ser Glu Lys Lys Ile Tyr Asp Val Glu
 85 90 95

Gln Thr Arg Tyr Lys Lys Ser Gly Leu His Phe Arg His Thr Asp Asn
 100 105 110

Thr Val Gln Trp Leu Arg Ala Met Glu Ser Ile Gly Leu Pro Lys Ile
 115 120 125

Phe Tyr Pro Glu Thr Thr Asp Val Tyr Asp Arg Lys Asn Ile Pro Arg
 130 135 140

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Met Ile Tyr Cys Ile His Ala Leu Ser Leu Tyr Leu Phe Lys Leu Gly
 145 150 155 160

Ile Ala Pro Gln Ile Gln Asp Leu Leu Gly Lys Val Asp Phe Thr Glu
 165 170 175

Glu Glu Ile Ser Asn Met Arg Lys Glu Leu Glu Lys Tyr Gly Ile Gln
 180 185 190

Met Pro Ser Phe Ser Lys Ile Gly Gly Ile Leu Ala Asn Glu Leu Ser
 195 200 205

Val Asp Glu Ala Ala Leu His Ala Ala Val Ile Ala Ile Asn Glu Ala
 210 215 220

Val Glu Lys Gly Ile Ala Glu Gln Thr Val Val Thr Leu Arg Asn Pro
 225 230 235 240

Asn Ala Val Leu Thr Leu Val Asp Asp Asn Leu Ala Pro Glu Tyr Gln
 245 250 255

Lys Glu Leu Trp Asp Ala Lys Lys Lys Lys Glu Glu Asn Ala Arg Leu
 260 265 270

Lys Asn Ser Cys Ile Ser Glu Glu Glu Arg Asp Ala Tyr Glu Glu Leu
 275 280 285

Leu Thr Gln Ala Glu Ile Gln Gly Asn Ile Asn Lys Val Asn Arg Gln
 290 295 300

Ala Ala Val Asp His Ile Asn Ala Val Ile Pro Glu Gly Asp Pro Glu
 305 310 315 320

Asn Thr Leu Leu Ala Leu Lys Lys Pro Glu Ala Gln Leu Pro Ala Val
 325 330 335

Tyr Pro Phe Ala Ala Ala Met Tyr Gln Asn Glu Leu Phe Asn Leu Gln
 340 345 350

Lys Gln Asn Thr Met Asn Tyr Leu Ala His Glu Glu Leu Leu Ile Ala
 355 360 365

Val Glu Met Leu Ser Ala Val Ala Leu Leu Asn Gln Ala Leu Glu Ser
 370 375 380

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Asn Asp Leu Val Ser Val Gln Asn Gln Leu Arg Ser Pro Ala Ile Gly
385 390 395 400

Leu Asn Asn Leu Asp Lys Ala Tyr Val Glu Arg Tyr Ala Asn Thr Leu
405 410 415

Leu Ser Val Lys Leu Glu Val Leu Ser Gln Gly Gln Asp Asn Leu Ser
420 425 430

Trp Asn Glu Ile Gln Asn Cys Ile Asp Met Val Asn Ala Gln Ile Gln
435 440 445

Glu Glu Asn Asp Arg Val Val Ala Val Gly Tyr Ile Asn Glu Ala Ile
450 455 460

Asp Glu Gly Asn Pro Leu Arg Thr Leu Glu Thr Leu Leu Leu Pro Thr
465 470 475 480

Ala Asn Ile Ser Asp Val Asp Pro Ala His Ala Gln His Tyr Gln Asp
485 490 495

Val Leu Tyr His Ala Lys Ser Gln Lys Leu Gly Asp Ser Glu Ser Val
500 505 510

Ser Lys Val Leu Trp Leu Asp Glu Ile Gln Gln Ala Val Asp Glu Ala
515 520 525

Asn Val Asp Glu Asp Arg Ala Lys Gln Trp Val Thr Leu Val Val Asp
530 535 540

Val Asn Gln Cys Leu Glu Gly Lys Lys Ser Ser Asp Ile Leu Ser Val
545 550 555 560

Leu Lys Ser Ser Thr Ser Asn Ala Asn Asp Ile Ile Pro Glu Cys Ala
565 570 575

Asp Lys Tyr Tyr Asp Ala Leu Val Lys Ala Lys Glu Leu Lys Ser Glu
580 585 590

Arg Val Ser Ser Asp Gly Ser Trp Leu Lys Leu Asn Leu His Lys Lys
595 600 605

Tyr Asp Tyr Tyr Tyr Asn Thr Asp Ser Lys Glu Ser Ser Trp Val Thr

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610					615					620					
Pro 625	Glu	Ser	Cys	Phe	Tyr 630	Lys	Glu	Ser	Trp	Leu 635	Thr	Gly	Lys	Glu	Ile 640
Glu	Asp	Ile	Ile	Glu 645	Glu	Val	Thr	Val	Gly 650	Tyr	Ile	Arg	Glu	Asn 655	Ile
Trp	Ser	Ala	Ser 660	Glu	Glu	Leu	Leu	Leu 665	Arg	Phe	Gln	Ala	Thr 670	Ser	Ser
Gly	Pro	Ile 675	Leu	Arg	Glu	Glu	Phe 680	Glu	Ala	Arg	Lys	Ser 685	Phe	Leu	His
Glu	Gln	Glu	Glu	Asn	Val	Val 695	Lys	Ile	Gln	Ala	Phe 700	Trp	Lys	Gly	Tyr
Lys 705	Gln	Arg	Lys	Glu	Tyr 710	Met	His	Arg	Arg	Gln 715	Thr	Phe	Ile	Asp	Asn 720
Thr	Asp	Ser	Val 725	Val	Lys	Ile	Gln	Ser	Trp 730	Phe	Arg	Met	Ala	Thr 735	Ala
Arg	Lys	Ser	Tyr 740	Leu	Ser	Arg	Leu	Gln 745	Tyr	Phe	Arg	Asp	His 750	Asn	Asn
Glu	Ile 755	Val	Lys	Ile	Gln	Ser	Leu 760	Leu	Arg	Ala	Asn	Lys 765	Ala	Arg	Asp
Asp 770	Tyr	Lys	Thr	Leu	Val	Gly 775	Ser	Glu	Asn	Pro 780	Pro	Leu	Thr	Val	Ile
Arg 785	Lys	Phe	Val	Tyr	Leu 790	Leu	Asp	Gln	Ser	Asp 795	Leu	Asp	Phe	Gln	Glu 800
Glu	Leu	Glu	Val	Ala 805	Arg	Leu	Arg	Glu	Glu 810	Val	Val	Thr	Lys	Ile 815	Arg
Ala	Asn	Gln	Gln	Leu	Glu	Lys	Asp	Leu 825	Asn	Leu	Met	Asp	Ile 830	Lys	Ile
Gly	Leu	Leu	Val	Lys	Asn	Arg	Ile 840	Thr	Leu	Glu	Asp	Val 845	Ile	Ser	His

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Ser Lys Lys Leu Asn Lys Lys Lys Gly Gly Glu Met Glu Ile Leu Asn
850 855 860

Asn Thr Asp Asn Gln Gly Ile Lys Ser Leu Ser Lys Glu Arg Arg Lys
865 870 875 880

Thr Leu Glu Thr Tyr Gln Gln Leu Phe Tyr Leu Leu Gln Thr Asn Pro
885 890 895

Leu Tyr Leu Ala Lys Leu Ile Phe Gln Met Pro Gln Asn Lys Ser Thr
900 905 910

Lys Phe Met Asp Thr Val Ile Phe Thr Leu Tyr Asn Tyr Ala Ser Asn
915 920 925

Gln Arg Glu Glu Tyr Leu Leu Leu Lys Leu Phe Lys Thr Ala Leu Glu
930 935 940

Glu Glu Ile Lys Ser Lys Val Asp Gln Val Gln Asp Ile Val Thr Gly
945 950 955 960

Asn Pro Thr Val Ile Lys Met Val Val Ser Phe Asn Arg Gly Ala Arg
965 970 975

Gly Gln Asn Thr Leu Arg Gln Leu Leu Ala Pro Val Val Lys Glu Ile
980 985 990

Ile Asp Asp Lys Ser Leu Ile Ile Asn Thr Asn Pro Val Glu Val Tyr
995 1000 1005

Lys Ala Trp Val Asn Gln Leu Glu Thr Gln Thr Gly Glu Ala Ser
1010 1015 1020

Lys Leu Pro Tyr Asp Val Thr Thr Glu Gln Ala Leu Thr Tyr Pro
1025 1030 1035

Glu Val Lys Asn Lys Leu Glu Ala Ser Ile Glu Asn Leu Arg Arg
1040 1045 1050

Val Thr Asp Lys Val Leu Asn Ser Ile Ile Ser Ser Leu Asp Leu
1055 1060 1065

Leu Pro Tyr Gly Leu Arg Tyr Ile Ala Lys Val Leu Lys Asn Ser
1070 1075 1080

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Ile His Glu Lys Phe Pro Asp Ala Thr Glu Asp Glu Leu Leu Lys
 1085 1090 1095

Ile Val Gly Asn Leu Leu Tyr Tyr Arg Tyr Met Asn Pro Ala Ile
 1100 1105 1110

Val Ala Pro Asp Gly Phe Asp Ile Ile Asp Met Thr Ala Gly Gly
 1115 1120 1125

Gln Ile Asn Ser Asp Gln Arg Arg Asn Leu Gly Ser Val Ala Lys
 1130 1135 1140

Val Leu Gln His Ala Ala Ser Asn Lys Leu Phe Glu Gly Glu Asn
 1145 1150 1155

Glu His Leu Ser Ser Met Asn Asn Tyr Leu Ser Glu Thr Tyr Gln
 1160 1165 1170

Glu Phe Arg Lys Tyr Phe Lys Glu Ala Cys Asn Val Pro Glu Pro
 1175 1180 1185

Glu Glu Lys Phe Asn Met Asp Lys Tyr Thr Asp Leu Val Thr Val
 1190 1195 1200

Ser Lys Pro Val Ile Tyr Ile Ser Ile Glu Glu Ile Ile Ser Thr
 1205 1210 1215

His Ser Leu Leu Leu Glu His Gln Asp Ala Ile Ala Pro Glu Lys
 1220 1225 1230

Asn Asp Leu Leu Ser Glu Leu Leu Gly Ser Leu Gly Glu Val Pro
 1235 1240 1245

Thr Val Glu Ser Phe Leu Gly Glu Gly Ala Val Asp Pro Asn Asp
 1250 1255 1260

Pro Asn Lys Ala Asn Thr Leu Ser Gln Leu Ser Lys Thr Glu Ile
 1265 1270 1275

Ser Leu Val Leu Thr Ser Lys Tyr Asp Ile Glu Asp Gly Glu Ala
 1280 1285 1290

Ile Asp Ser Arg Ser Leu Met Ile Lys Thr Lys Lys Leu Ile Ile
 1295 1300 1305

Asp	Val	Ile	Arg	Asn	Gln	Pro	Gly	Asn	Thr	Leu	Thr	Glu	Ile	Leu
1310						1315						1320		
Glu	Thr	Pro	Ala	Thr	Ala	Gln	Gln	Glu	Val	Asp	His	Ala	Thr	Asp
1325						1330					1335			
Met	Val	Ser	Arg	Ala	Met	Ile	Asp	Ser	Arg	Thr	Pro	Glu	Glu	Met
1340						1345					1350			
Lys	His	Ser	Gln	Ser	Met	Ile	Glu	Asp	Ala	Gln	Leu	Pro	Leu	Glu
1355						1360					1365			
Gln	Lys	Lys	Arg	Lys	Ile	Gln	Arg	Asn	Leu	Arg	Thr	Leu	Glu	Gln
1370						1375					1380			
Thr	Gly	His	Val	Ser	Ser	Glu	Asn	Lys	Tyr	Gln	Asp	Ile	Leu	Asn
1385						1390					1395			
Glu	Ile	Ala	Lys	Asp	Ile	Arg	Asn	Gln	Arg	Ile	Tyr	Arg	Lys	Leu
1400						1405					1410			
Arg	Lys	Ala	Glu	Leu	Ala	Lys	Leu	Gln	Gln	Thr	Leu	Asn	Ala	Leu
1415						1420					1425			
Asn	Lys	Lys	Ala	Ala	Phe	Tyr	Glu	Glu	Gln	Ile	Asn	Tyr	Tyr	Asp
1430						1435					1440			
Thr	Tyr	Ile	Lys	Thr	Cys	Leu	Asp	Asn	Leu	Lys	Arg	Lys	Asn	Thr
1445						1450					1455			
Arg	Arg	Ser	Ile	Lys	Leu	Asp	Gly	Lys	Gly	Glu	Pro	Lys	Gly	Ala
1460						1465					1470			
Lys	Arg	Ala	Lys	Pro	Val	Lys	Tyr	Thr	Ala	Ala	Lys	Leu	His	Glu
1475						1480					1485			
Lys	Gly	Val	Leu	Leu	Asp	Ile	Asp	Asp	Leu	Gln	Thr	Asn	Gln	Phe
1490						1495					1500			
Lys	Asn	Val	Thr	Phe	Asp	Ile	Ile	Ala	Thr	Glu	Asp	Val	Gly	Ile
1505						1510					1515			

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Phe Asp Val Arg Ser Lys Phe Leu Gly Val Glu Met Glu Lys Val
 1520 1525 1530

Gln Leu Asn Ile Gln Asp Leu Leu Gln Met Gln Tyr Glu Gly Val
 1535 1540 1545

Ala Val Met Lys Met Phe Asp Lys Val Lys Val Asn Val Asn Leu
 1550 1555 1560

Leu Ile Tyr Leu Leu Asn Lys Lys Phe Tyr Gly Lys
 1565 1570 1575

<210> 90

<211> 713

<212> PRT

<213> Homo sapiens

<400> 90

Leu Ala Cys Phe Leu Asp Lys His His Asp Ile Ile Ile Ile Asp His
 1 5 10 15

Arg Asn Pro Arg Gln Leu Asp Ala Glu Ala Leu Cys Arg Ser Ile Arg
 20 25 30

Ser Ser Lys Leu Ser Glu Asn Thr Val Ile Val Gly Val Val Arg Arg
 35 40 45

Val Asp Arg Glu Glu Leu Ser Val Met Pro Phe Ile Ser Ala Gly Phe
 50 55 60

Thr Arg Arg Tyr Val Glu Asn Pro Asn Ile Met Ala Cys Tyr Asn Glu
 65 70 75 80

Leu Leu Gln Leu Glu Phe Gly Glu Val Arg Ser Gln Leu Lys Leu Arg
 85 90 95

Ala Cys Asn Ser Val Phe Thr Ala Leu Glu Asn Ser Glu Asp Ala Ile
 100 105 110

Glu Ile Thr Ser Glu Asp Arg Phe Ile Gln Tyr Ala Asn Pro Ala Phe
 115 120 125

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Glu Thr Thr Met Gly Tyr Gln Ser Gly Glu Leu Ile Gly Lys Glu Leu
 130 135 140

Gly Glu Val Pro Ile Asn Glu Lys Lys Ala Asp Leu Leu Asp Thr Ile
 145 150 155 160

Asn Ser Cys Ile Arg Ile Gly Lys Glu Trp Gln Gly Ile Tyr Tyr Ala
 165 170 175

Lys Lys Lys Asn Gly Asp Asn Ile Gln Gln Asn Val Lys Ile Ile Pro
 180 185 190

Val Ile Gly Gln Gly Gly Lys Ile Arg His Tyr Val Ser Ile Ile Arg
 195 200 205

Val Cys Asn Gly Asn Asn Lys Ala Glu Lys Ile Ser Glu Cys Val Gln
 210 215 220

Ser Asp Thr Arg Thr Asp Asn Gln Thr Gly Lys His Lys Asp Arg Arg
 225 230 235 240

Lys Gly Ser Leu Asp Val Lys Ala Val Ala Ser Arg Ala Thr Glu Val
 245 250 255

Ser Ser Gln Arg Arg His Ser Ser Met Ala Arg Ile His Ser Met Thr
 260 265 270

Ile Glu Ala Pro Ile Thr Lys Val Ile Asn Val Ile Asn Ala Ala Gln
 275 280 285

Glu Ser Ser Pro Met Pro Val Thr Glu Ala Leu Asp Arg Val Leu Glu
 290 295 300

Ile Leu Arg Thr Thr Glu Leu Tyr Ser Pro Gln Phe Gly Ala Lys Asp
 305 310 315 320

Asp Asp Pro His Ala Asn Asp Leu Val Gly Gly Leu Met Ser Asp Gly
 325 330 335

Leu Arg Arg Leu Ser Gly Asn Glu Tyr Val Leu Ser Thr Lys Asn Thr
 340 345 350

Gln Met Val Ser Ser Asn Ile Ile Thr Pro Ile Ser Leu Asp Asp Val
 355 360 365

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Pro Pro Arg Ile Ala Arg Ala Met Glu Asn Glu Glu Tyr Trp Asp Phe
370 375 380

Asp Ile Phe Glu Leu Glu Ala Ala Thr His Asn Arg Pro Leu Ile Tyr
385 390 395 400

Leu Gly Leu Lys Met Phe Ala Arg Phe Gly Ile Cys Glu Phe Leu His
405 410 415

Cys Ser Glu Ser Thr Leu Arg Ser Trp Leu Gln Ile Ile Glu Ala Asn
420 425 430

Tyr His Ser Ser Asn Pro Tyr His Asn Ser Thr His Ser Ala Asp Val
435 440 445

Leu His Ala Thr Ala Tyr Phe Leu Ser Lys Glu Arg Ile Lys Glu Thr
450 455 460

Leu Asp Pro Ile Asp Glu Val Ala Ala Leu Ile Ala Ala Thr Ile His
465 470 475 480

Asp Val Asp His Pro Gly Arg Thr Asn Ser Phe Leu Cys Asn Ala Gly
485 490 495

Ser Glu Leu Ala Ile Leu Tyr Asn Asp Thr Ala Val Leu Glu Ser His
500 505 510

His Ala Ala Leu Ala Phe Gln Leu Thr Thr Gly Asp Asp Lys Cys Asn
515 520 525

Ile Phe Lys Asn Met Glu Arg Asn Asp Tyr Arg Thr Leu Arg Gln Gly
530 535 540

Ile Ile Asp Met Val Leu Ala Thr Glu Met Thr Lys His Phe Glu His
545 550 555 560

Val Asn Lys Phe Val Asn Ser Ile Asn Lys Pro Leu Ala Thr Leu Glu
565 570 575

Glu Asn Gly Glu Thr Asp Lys Asn Gln Glu Val Ile Asn Thr Met Leu
580 585 590

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Arg Thr Pro Glu Asn Arg Thr Leu Ile Lys Arg Met Leu Ile Lys Cys
 595 600 605

Ala Asp Val Ser Asn Pro Cys Arg Pro Leu Gln Tyr Cys Ile Glu Trp
 610 615 620

Ala Ala Arg Ile Ser Glu Glu Tyr Phe Ser Gln Thr Asp Glu Glu Lys
 625 630 635 640

Gln Gln Gly Leu Pro Val Val Met Pro Val Phe Asp Arg Asn Thr Cys
 645 650 655

Ser Ile Pro Lys Ser Gln Ile Ser Phe Ile Asp Tyr Phe Ile Thr Asp
 660 665 670

Met Phe Asp Ala Trp Asp Ala Phe Val Asp Leu Pro Asp Leu Met Gln
 675 680 685

His Leu Asp Asn Asn Phe Lys Tyr Trp Lys Gly Leu Asp Glu Met Lys
 690 695 700

Leu Arg Asn Leu Arg Pro Pro Pro Glu
 705 710

<210> 91

<211> 323

<212> PRT

<213> Homo sapiens

<400> 91

Met Asp Met Trp Thr Ala Leu Leu Ile Leu Gln Ala Leu Leu Leu Pro
 1 5 10 15

Ser Leu Ala Asp Gly Ala Thr Pro Ala Leu Arg Phe Val Ala Val Gly
 20 25 30

Asp Trp Gly Gly Val Pro Asn Ala Pro Phe His Thr Gly Pro Glu Met
 35 40 45

Ala Asn Ala Lys Glu Ile Ala Arg Thr Val Gln Ile Leu Gly Ala Asp
 50 55 60

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Phe Ile Leu Ser Leu Gly Asp Asn Phe Tyr Phe Thr Gly Val Gln Asp
 65 70 75 80

Ile Asn Asp Lys Arg Phe Gln Glu Thr Phe Glu Asp Val Phe Ser Asp
 85 90 95

Arg Ser Leu Arg Lys Val Pro Trp Tyr Val Leu Ala Gly Asn His Asp
 100 105 110

His Leu Gly Asn Val Ser Ala Gln Ile Ala Tyr Ser Lys Ile Ser Lys
 115 120 125

Arg Trp Asn Phe Pro Ser Pro Phe Tyr Arg Leu His Phe Lys Ile Pro
 130 135 140

Gln Thr Asn Val Ser Val Ala Ile Phe Met Leu Asp Thr Val Thr Leu
 145 150 155 160

Cys Gly Asn Ser Asp Asp Phe Leu Ser Gln Gln Pro Glu Arg Pro Arg
 165 170 175

Leu Thr Ala Arg Thr Gln Leu Ser Trp Leu Lys Lys Gln Leu Ala Ala
 180 185 190

Ala Arg Glu Asp Tyr Val Leu Val Ala Gly His Tyr Pro Val Trp Ser
 195 200 205

Ile Ala Glu His Gly Pro Thr His Cys Leu Val Lys Gln Leu Arg Pro
 210 215 220

Leu Leu Ala Thr Tyr Gly Val Thr Ala Tyr Leu Cys Gly His Asp His
 225 230 235 240

Asn Leu Gln Tyr Leu Gln Asp Glu Asn Gly Val Gly Tyr Val Leu Ser
 245 250 255

Gly Ala Gly Asn Phe Met Asp Pro Ser Lys Arg His Gln Arg Lys Val
 260 265 270

Pro Asn Gly Tyr Leu Arg Phe His Tyr Gly Thr Glu Asp Ser Leu Gly
 275 280 285

Gly Phe Ala Tyr Val Glu Ile Ser Ser Lys Glu Met Thr Val Thr Tyr
 290 295 300

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Ile Glu Ala Ser Gly Lys Ser Leu Phe Lys Thr Arg Leu Pro Arg Arg
 305 310 315 320

Ala Arg Pro

<210> 92

<211> 669

<212> PRT

<213> Homo sapiens

<400> 92

Met Met Arg Leu Arg Gly Ser Gly Met Leu Arg Asp Leu Leu Leu Arg
 1 5 10 15

Ser Pro Ala Gly Val Ser Ala Thr Leu Arg Arg Ala Gln Pro Leu Val
 20 25 30

Thr Leu Cys Arg Arg Pro Arg Gly Gly Gly Arg Pro Ala Ala Gly Pro
 35 40 45

Ala Ala Ala Ala Arg Leu His Pro Trp Trp Gly Gly Gly Gly Trp Pro
 50 55 60

Ala Glu Pro Leu Ala Arg Gly Leu Ser Ser Ser Pro Ser Glu Ile Leu
 65 70 75 80

Gln Glu Leu Gly Lys Gly Ser Thr His Pro Gln Pro Gly Val Ser Pro
 85 90 95

Pro Ala Ala Pro Ala Ala Pro Gly Pro Lys Asp Gly Pro Gly Glu Thr
 100 105 110

Asp Ala Phe Gly Asn Ser Glu Gly Lys Glu Leu Val Ala Ser Gly Glu
 115 120 125

Asn Lys Ile Lys Gln Gly Leu Leu Pro Ser Leu Glu Asp Leu Leu Phe
 130 135 140

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Tyr Thr Ile Ala Glu Gly Gln Glu Lys Ile Pro Val His Lys Phe Ile
 145 150 155 160

Thr Ala Leu Lys Ser Thr Gly Leu Arg Thr Ser Asp Pro Arg Leu Lys
 165 170 175

Glu Cys Met Asp Met Leu Arg Leu Thr Leu Gln Thr Thr Ser Asp Gly
 180 185 190

Val Met Leu Asp Lys Asp Leu Phe Lys Lys Cys Val Gln Ser Asn Ile
 195 200 205

Val Leu Leu Thr Gln Ala Phe Arg Arg Lys Phe Val Ile Pro Asp Phe
 210 215 220

Met Ser Phe Thr Ser His Ile Asp Glu Leu Tyr Glu Ser Ala Lys Lys
 225 230 235 240

Gln Ser Gly Gly Lys Val Ala Asp Tyr Ile Pro Gln Leu Ala Lys Phe
 245 250 255

Ser Pro Asp Leu Trp Gly Val Ser Val Cys Thr Val Asp Gly Gln Arg
 260 265 270

His Ser Thr Gly Asp Thr Lys Val Pro Phe Cys Leu Gln Ser Cys Val
 275 280 285

Lys Pro Leu Lys Tyr Ala Ile Ala Val Asn Asp Leu Gly Thr Glu Tyr
 290 295 300

Val His Arg Tyr Val Gly Lys Glu Pro Ser Gly Leu Arg Phe Asn Lys
 305 310 315 320

Leu Phe Leu Asn Glu Asp Asp Lys Pro His Asn Pro Met Val Asn Ala
 325 330 335

Gly Ala Ile Val Val Thr Ser Leu Ile Lys Gln Gly Val Asn Asn Ala
 340 345 350

Glu Lys Phe Asp Tyr Val Met Gln Phe Leu Asn Lys Met Ala Gly Asn
 355 360 365

Glu Tyr Val Gly Phe Ser Asn Ala Thr Phe Gln Ser Glu Arg Glu Ser
 370 375 380

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Gly Asp Arg Asn Phe Ala Ile Gly Tyr Tyr Leu Lys Glu Lys Lys Cys
 385 390 395 400

Phe Pro Glu Gly Thr Asp Met Val Gly Ile Leu Asp Phe Tyr Phe Gln
 405 410 415

Leu Cys Ser Ile Glu Val Thr Cys Glu Ser Ala Ser Val Met Ala Ala
 420 425 430

Thr Leu Ala Asn Gly Gly Phe Cys Pro Ile Thr Gly Glu Arg Val Leu
 435 440 445

Ser Pro Glu Ala Val Arg Asn Thr Leu Ser Leu Met His Ser Cys Gly
 450 455 460

Met Tyr Asp Phe Ser Gly Gln Phe Ala Phe His Val Gly Leu Pro Ala
 465 470 475 480

Lys Ser Gly Val Ala Gly Gly Ile Leu Leu Val Val Pro Asn Val Met
 485 490 495

Gly Met Met Cys Trp Ser Pro Pro Leu Asp Lys Met Gly Asn Ser Val
 500 505 510

Lys Gly Ile His Phe Cys His Asp Leu Val Ser Leu Cys Asn Phe His
 515 520 525

Asn Tyr Asp Asn Leu Arg His Phe Ala Lys Lys Leu Asp Pro Arg Arg
 530 535 540

Glu Gly Gly Asp Gln Arg Val Lys Ser Val Ile Asn Leu Leu Phe Ala
 545 550 555 560

Ala Tyr Thr Gly Asp Val Ser Ala Leu Arg Arg Phe Ala Leu Ser Ala
 565 570 575

Met Asp Met Glu Gln Arg Asp Tyr Asp Ser Arg Thr Ala Leu His Val
 580 585 590

Ala Ala Ala Glu Gly His Val Glu Val Val Lys Phe Leu Leu Glu Ala
 595 600 605

Cys Lys Val Asn Pro Phe Pro Lys Asp Arg Trp Asn Asn Thr Pro Met
 610 615 620

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Asp Glu Ala Leu His Phe Gly His His Asp Val Phe Lys Ile Leu Gln
 625 630 635 640

Glu Tyr Gln Val Gln Tyr Thr Pro Gln Gly Asp Ser Asp Asn Gly Lys
 645 650 655

Glu Asn Gln Thr Val His Lys Asn Leu Asp Gly Leu Leu
 660 665

<210> 93

<211> 383

<212> PRT

<213> Homo sapiens

<400> 93

Met Gly Val Lys Ala Ser Gln Thr Gly Phe Val Val Leu Val Leu Leu
 1 5 10 15

Gln Cys Cys Ser Ala Tyr Lys Leu Val Cys Tyr Tyr Thr Ser Trp Ser
 20 25 30

Gln Tyr Arg Glu Gly Asp Gly Ser Cys Phe Pro Asp Ala Leu Asp Arg
 35 40 45

Phe Leu Cys Thr His Ile Ile Tyr Ser Phe Ala Asn Ile Ser Asn Asp
 50 55 60

His Ile Asp Thr Trp Glu Trp Asn Asp Val Thr Leu Tyr Gly Met Leu
 65 70 75 80

Asn Thr Leu Lys Asn Arg Asn Pro Asn Leu Lys Thr Leu Leu Ser Val
 85 90 95

Gly Gly Trp Asn Phe Gly Ser Gln Arg Phe Ser Lys Ile Ala Ser Asn
 100 105 110

Thr Gln Ser Arg Arg Thr Phe Ile Lys Ser Val Pro Pro Phe Leu Arg
 115 120 125

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Thr His Gly Phe Asp Gly Leu Asp Leu Ala Trp Leu Tyr Pro Gly Arg
 130 135 140

Arg Asp Lys Gln His Phe Thr Thr Leu Ile Lys Glu Met Lys Ala Glu
 145 150 155 160

Phe Ile Lys Glu Ala Gln Pro Gly Lys Lys Gln Leu Leu Leu Ser Ala
 165 170 175

Ala Leu Ser Ala Gly Lys Val Thr Ile Asp Ser Ser Tyr Asp Ile Ala
 180 185 190

Lys Ile Ser Gln His Leu Asp Phe Ile Ser Ile Met Thr Tyr Asp Phe
 195 200 205

His Gly Ala Trp Arg Gly Thr Thr Gly His His Ser Pro Leu Phe Arg
 210 215 220

Gly Gln Glu Asp Ala Ser Pro Asp Arg Phe Ser Asn Thr Asp Tyr Ala
 225 230 235 240

Val Gly Tyr Met Leu Arg Leu Gly Ala Pro Ala Ser Lys Leu Val Met
 245 250 255

Gly Ile Pro Thr Phe Gly Arg Ser Phe Thr Leu Ala Ser Ser Glu Thr
 260 265 270

Gly Val Gly Ala Pro Ile Ser Gly Pro Gly Ile Pro Gly Arg Phe Thr
 275 280 285

Lys Glu Ala Gly Thr Leu Ala Tyr Tyr Glu Ile Cys Asp Phe Leu Arg
 290 295 300

Gly Ala Thr Val His Arg Thr Leu Gly Gln Gln Val Pro Tyr Ala Thr
 305 310 315 320

Lys Gly Asn Gln Trp Val Gly Tyr Asp Asp Gln Glu Ser Val Lys Ser
 325 330 335

Lys Val Gln Tyr Leu Lys Asp Arg Gln Leu Ala Gly Ala Met Val Trp
 340 345 350

Ala Leu Asp Leu Asp Asp Phe Gln Gly Ser Phe Cys Gly Gln Asp Leu
 355 360 365

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Arg Phe Pro Leu Thr Asn Ala Ile Lys Asp Ala Leu Ala Ala Thr
 370 375 380

<210> 94

<211> 433

<212> PRT

<213> Homo sapiens

<400> 94

Met Val Trp Lys Val Ala Val Phe Leu Ser Val Ala Leu Gly Ile Gly
 1 5 10 15

Ala Val Pro Ile Asp Asp Pro Glu Asp Gly Gly Lys His Trp Ala Val
 20 25 30

Ile Val Ala Gly Ser Asn Gly Trp Tyr Asn Tyr Arg His Gln Ala Asp
 35 40 45

Ala Cys His Ala Tyr Gln Ile Ile His Arg Asn Gly Ile Pro Asp Glu
 50 55 60

Gln Ile Val Val Met Met Tyr Asp Asp Ile Ala Tyr Ser Glu Asp Asn
 65 70 75 80

Pro Thr Pro Gly Ile Val Ile Asn Arg Pro Asn Gly Thr Asp Val Tyr
 85 90 95

Gln Gly Val Pro Lys Asp Tyr Thr Gly Glu Asp Val Thr Pro Gln Asn
 100 105 110

Phe Leu Ala Val Leu Arg Gly Asp Ala Glu Ala Val Lys Gly Ile Gly
 115 120 125

Ser Gly Lys Val Leu Lys Ser Gly Pro Gln Asp His Val Phe Ile Tyr
 130 135 140

Phe Thr Asp His Gly Ser Thr Gly Ile Leu Val Phe Pro Asn Glu Asp
 145 150 155 160

Leu His Val Lys Asp Leu Asn Glu Thr Ile His Tyr Met Tyr Lys His
 165 170 175

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Lys Met Tyr Arg Lys Met Val Phe Tyr Ile Glu Ala Cys Glu Ser Gly
 180 185 190

Ser Met Met Asn His Leu Pro Asp Asn Ile Asn Val Tyr Ala Thr Thr
 195 200 205

Ala Ala Asn Pro Arg Glu Ser Ser Tyr Ala Cys Tyr Tyr Asp Glu Lys
 210 215 220

Arg Ser Thr Tyr Leu Gly Asp Trp Tyr Ser Val Asn Trp Met Glu Asp
 225 230 235 240

Ser Asp Val Glu Asp Leu Thr Lys Glu Thr Leu His Lys Gln Tyr His
 245 250 255

Leu Val Lys Ser His Thr Asn Thr Ser His Val Met Gln Tyr Gly Asn
 260 265 270

Lys Thr Ile Ser Thr Met Lys Val Met Gln Phe Gln Gly Met Lys Arg
 275 280 285

Lys Ala Ser Ser Pro Val Pro Leu Pro Pro Val Thr His Leu Asp Leu
 290 295 300

Thr Pro Ser Pro Asp Val Pro Leu Thr Ile Met Lys Arg Lys Leu Met
 305 310 315 320

Asn Thr Asn Asp Leu Glu Glu Ser Arg Gln Leu Thr Glu Glu Ile Gln
 325 330 335

Arg His Leu Asp Ala Arg His Leu Ile Glu Lys Ser Val Arg Lys Ile
 340 345 350

Val Ser Leu Leu Ala Ala Ser Glu Ala Glu Val Glu Gln Leu Leu Ser
 355 360 365

Glu Arg Ala Pro Leu Thr Gly His Ser Cys Tyr Pro Glu Ala Leu Leu
 370 375 380

His Phe Arg Thr His Cys Phe Asn Trp His Ser Pro Thr Tyr Glu Tyr
 385 390 395 400

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Ala Leu Arg His Leu Tyr Val Leu Val Asn Leu Cys Glu Lys Pro Tyr
 405 410 415

Pro Leu His Arg Ile Lys Leu Ser Met Asp His Val Cys Leu Gly His
 420 425 430

Tyr

<210> 95

<211> 333

<212> PRT

<213> Homo sapiens

<400> 95

Met Asn Pro Thr Leu Ile Leu Ala Ala Phe Cys Leu Gly Ile Ala Ser
 1 5 10 15

Ala Thr Leu Thr Phe Asp His Ser Leu Glu Ala Gln Trp Thr Lys Trp
 20 25 30

Lys Ala Met His Asn Arg Leu Tyr Gly Met Asn Glu Glu Gly Trp Arg
 35 40 45

Arg Ala Val Trp Glu Lys Asn Met Lys Met Ile Glu Leu His Asn Gln
 50 55 60

Glu Tyr Arg Glu Gly Lys His Ser Phe Thr Met Ala Met Asn Ala Phe
 65 70 75 80

Gly Asp Met Thr Ser Glu Glu Phe Arg Gln Val Met Asn Gly Phe Gln
 85 90 95

Asn Arg Lys Pro Arg Lys Gly Lys Val Phe Gln Glu Pro Leu Phe Tyr
 100 105 110

Glu Ala Pro Arg Ser Val Asp Trp Arg Glu Lys Gly Tyr Val Thr Pro
 115 120 125

Val Lys Asn Gln Gly Gln Cys Gly Ser Cys Trp Ala Phe Ser Ala Thr
 130 135 140

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Gly Ala Leu Glu Gly Gln Met Phe Arg Lys Thr Gly Arg Leu Ile Ser
 145 150 155 160

Leu Ser Glu Gln Asn Leu Val Asp Cys Ser Gly Pro Gln Gly Asn Glu
 165 170 175

Gly Cys Asn Gly Gly Leu Met Asp Tyr Ala Phe Gln Tyr Val Gln Asp
 180 185 190

Asn Gly Gly Leu Asp Ser Glu Glu Ser Tyr Pro Tyr Glu Ala Thr Glu
 195 200 205

Glu Ser Cys Lys Tyr Asn Pro Lys Tyr Ser Val Ala Asn Asp Thr Gly
 210 215 220

Phe Val Asp Ile Pro Lys Gln Glu Lys Ala Leu Met Lys Ala Val Ala
 225 230 235 240

Thr Val Gly Pro Ile Ser Val Ala Ile Asp Ala Gly His Glu Ser Phe
 245 250 255

Leu Phe Tyr Lys Glu Gly Ile Tyr Phe Glu Pro Asp Cys Ser Ser Glu
 260 265 270

Asp Met Asp His Gly Val Leu Val Val Gly Tyr Gly Phe Glu Ser Thr
 275 280 285

Glu Ser Asp Asn Asn Lys Tyr Trp Leu Val Lys Asn Ser Trp Gly Glu
 290 295 300

Glu Trp Gly Met Gly Gly Tyr Val Lys Met Ala Lys Asp Arg Arg Asn
 305 310 315 320

His Cys Gly Ile Ala Ser Ala Ala Ser Tyr Pro Thr Val
 325 330

<210> 96

<211> 175

<212> PRT

<213> Homo sapiens

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<400> 96

Met Thr Asp Cys Glu Phe Gly Tyr Ile Tyr Arg Leu Ala Gln Asp Tyr
 1 5 10 15

Leu Gln Cys Val Leu Gln Ile Pro Gln Pro Gly Ser Gly Pro Ser Lys
 20 25 30

Thr Ser Arg Val Leu Gln Asn Val Ala Phe Ser Val Gln Lys Glu Val
 35 40 45

Glu Lys Asn Leu Lys Ser Cys Leu Asp Asn Val Asn Val Val Ser Val
 50 55 60

Asp Thr Ala Arg Thr Leu Phe Asn Gln Val Met Glu Lys Glu Phe Glu
 65 70 75 80

Asp Gly Ile Ile Asn Trp Gly Arg Ile Val Thr Ile Phe Ala Phe Glu
 85 90 95

Gly Ile Leu Ile Lys Lys Leu Leu Arg Gln Gln Ile Ala Pro Asp Val
 100 105 110

Asp Thr Tyr Lys Glu Ile Ser Tyr Phe Val Ala Glu Phe Ile Met Asn
 115 120 125

Asn Thr Gly Glu Trp Ile Arg Gln Asn Gly Gly Trp Glu Asn Gly Phe
 130 135 140

Val Lys Lys Phe Glu Pro Lys Ser Gly Trp Met Thr Phe Leu Glu Val
 145 150 155 160

Thr Gly Lys Ile Cys Glu Met Leu Ser Leu Leu Lys Gln Tyr Cys
 165 170 175

<210> 97

<211> 732

<212> PRT

<213> Homo sapiens

<400> 97

Met Thr Glu Gly Thr Cys Leu Arg Arg Arg Gly Gly Pro Tyr Lys Thr

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1	5	10	15
Glu Pro Ala Thr Asp Leu Gly Arg Trp Arg Leu Asn Cys Glu Arg Gly	20	25	30
Arg Gln Thr Trp Thr Tyr Leu Gln Asp Glu Arg Ala Gly Arg Glu Gln	35	40	45
Thr Gly Leu Glu Ala Tyr Ala Leu Gly Leu Asp Thr Lys Asn Tyr Phe	50	55	60
Lys Asp Leu Pro Lys Ala His Thr Ala Phe Glu Gly Ala Leu Asn Gly	65	70	75
Met Thr Phe Tyr Val Gly Leu Gln Ala Glu Asp Gly His Trp Thr Gly	85	90	95
Asp Tyr Gly Gly Pro Leu Phe Leu Leu Pro Gly Leu Leu Ile Thr Cys	100	105	110
His Val Ala Arg Ile Pro Leu Pro Ala Gly Tyr Arg Glu Glu Ile Val	115	120	125
Arg Tyr Leu Arg Ser Val Gln Leu Pro Asp Gly Gly Trp Gly Leu His	130	135	140
Ile Glu Asp Lys Ser Thr Val Phe Gly Thr Ala Leu Asn Tyr Val Ser	145	150	155
Leu Arg Ile Leu Gly Val Gly Pro Asp Asp Pro Asp Leu Val Arg Ala	165	170	175
Arg Asn Ile Leu His Lys Lys Gly Gly Ala Val Ala Ile Pro Ser Trp	180	185	190
Gly Lys Phe Trp Leu Ala Val Leu Asn Val Tyr Ser Trp Glu Gly Leu	195	200	205
Asn Thr Leu Phe Pro Glu Met Trp Leu Phe Pro Asp Trp Ala Pro Ala	210	215	220
His Pro Ser Thr Leu Trp Cys His Cys Arg Gln Val Tyr Leu Pro Met	225	230	235
			240

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Ser Tyr Cys Tyr Ala Val Arg Leu Ser Ala Ala Glu Asp Pro Leu Val
245 250 255

Gln Ser Leu Arg Gln Glu Leu Tyr Val Glu Asp Phe Ala Ser Ile Asp
260 265 270

Trp Leu Ala Gln Arg Asn Asn Val Ala Pro Asp Glu Leu Tyr Thr Pro
275 280 285

His Ser Trp Leu Leu Arg Val Val Tyr Ala Leu Leu Asn Leu Tyr Glu
290 295 300

His His His Ser Ala His Leu Arg Gln Arg Ala Val Gln Lys Leu Tyr
305 310 315 320

Glu His Ile Val Ala Asp Asp Arg Phe Thr Lys Ser Ile Ser Ile Gly
325 330 335

Pro Ile Ser Lys Thr Ile Asn Met Leu Val Arg Trp Tyr Val Asp Gly
340 345 350

Pro Ala Ser Thr Ala Phe Gln Glu His Val Ser Arg Ile Pro Asp Tyr
355 360 365

Leu Trp Met Gly Leu Asp Gly Met Lys Met Gln Gly Thr Asn Gly Ser
370 375 380

Gln Ile Trp Asp Thr Ala Phe Ala Ile Gln Ala Leu Leu Glu Ala Gly
385 390 395 400

Gly His His Arg Pro Glu Phe Ser Ser Cys Leu Gln Lys Ala His Glu
405 410 415

Phe Leu Arg Leu Ser Gln Val Pro Asp Asn Pro Pro Asp Tyr Gln Lys
420 425 430

Tyr Tyr Arg Gln Met Arg Lys Gly Gly Phe Ser Phe Ser Thr Leu Asp
435 440 445

Cys Gly Trp Ile Val Ser Asp Cys Thr Ala Glu Ala Leu Lys Ala Val
450 455 460

Leu Leu Leu Gln Glu Lys Cys Pro His Val Thr Glu His Ile Pro Arg
465 470 475 480

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Glu Arg Leu Cys Asp Ala Val Ala Val Leu Leu Asn Met Arg Asn Pro
 485 490 495

Asp Gly Gly Phe Ala Thr Tyr Glu Thr Lys Arg Gly Gly His Leu Leu
 500 505 510

Glu Leu Leu Asn Pro Ser Glu Val Phe Gly Asp Ile Met Ile Asp Tyr
 515 520 525

Thr Tyr Val Glu Cys Thr Ser Ala Val Met Gln Ala Leu Lys Tyr Phe
 530 535 540

His Lys Arg Phe Pro Glu His Arg Ala Ala Glu Ile Arg Glu Thr Leu
 545 550 555 560

Thr Gln Gly Leu Glu Phe Cys Arg Arg Gln Gln Arg Ala Asp Gly Ser
 565 570 575

Trp Glu Gly Ser Trp Gly Val Cys Phe Thr Tyr Gly Thr Trp Phe Gly
 580 585 590

Leu Glu Ala Phe Ala Cys Met Gly Gln Thr Tyr Arg Asp Gly Thr Ala
 595 600 605

Cys Ala Glu Val Ser Arg Ala Cys Asp Phe Leu Leu Ser Arg Gln Met
 610 615 620

Ala Asp Gly Gly Trp Gly Glu Asp Phe Glu Ser Cys Glu Glu Arg Arg
 625 630 635 640

Tyr Leu Gln Ser Ala Gln Ser Gln Ile His Asn Thr Cys Trp Ala Met
 645 650 655

Met Gly Leu Met Ala Val Arg His Pro Asp Ile Glu Ala Gln Glu Arg
 660 665 670

Gly Val Arg Cys Leu Leu Glu Lys Gln Leu Pro Asn Gly Asp Trp Pro
 675 680 685

Gln Glu Asn Ile Ala Gly Val Phe Asn Lys Ser Cys Ala Ile Ser Tyr
 690 695 700

Thr Ser Tyr Arg Asn Ile Phe Pro Ile Trp Ala Leu Gly Arg Phe Ser
 705 710 715 720

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Gln Leu Tyr Pro Glu Arg Ala Leu Ala Gly His Pro
725 730

<210> 98

<211> 228

<212> PRT

<213> Homo sapiens

<400> 98

Met Met Pro Glu Ile Asn Thr Asn His Leu Asp Lys Gln Gln Val Gln
1 5 10 15

Leu Leu Ala Glu Met Cys Ile Leu Ile Asp Glu Asn Asp Asn Lys Ile
20 25 30

Gly Ala Glu Thr Lys Lys Asn Cys His Leu Asn Glu Asn Ile Glu Lys
35 40 45

Gly Leu Leu His Arg Ala Phe Ser Val Phe Leu Phe Asn Thr Glu Asn
50 55 60

Lys Leu Leu Leu Gln Gln Arg Ser Asp Ala Lys Ile Thr Phe Pro Gly
65 70 75 80

Cys Phe Thr Asn Thr Cys Cys Ser His Pro Leu Ser Asn Pro Ala Glu
85 90 95

Leu Glu Glu Ser Asp Ala Leu Gly Val Arg Arg Ala Ala Gln Arg Arg
100 105 110

Leu Lys Ala Glu Leu Gly Ile Pro Leu Glu Glu Val Pro Pro Glu Glu
115 120 125

Ile Asn Tyr Leu Thr Arg Ile His Tyr Lys Ala Gln Ser Asp Gly Ile
130 135 140

Trp Gly Glu His Glu Ile Asp Tyr Ile Leu Leu Val Arg Lys Asn Val
145 150 155 160

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Thr Leu Asn Pro Asp Pro Asn Glu Ile Lys Ser Tyr Cys Tyr Val Ser
 165 170 175

Lys Glu Glu Leu Lys Glu Leu Leu Lys Lys Ala Ala Ser Gly Glu Ile
 180 185 190

Lys Ile Thr Pro Trp Phe Lys Ile Ile Ala Ala Thr Phe Leu Phe Lys
 195 200 205

Trp Trp Asp Asn Leu Asn His Leu Asn Gln Phe Val Asp His Glu Lys
 210 215 220

Ile Tyr Arg Met
 225

<210> 99

<211> 302

<212> PRT

<213> Homo sapiens

<400> 99

Met Ala Trp Lys Arg Leu Gly Ala Leu Val Met Phe Pro Leu Gln Met
 1 5 10 15

Ile Tyr Leu Val Val Lys Ala Ala Val Gly Leu Val Leu Pro Ala Lys
 20 25 30

Leu Arg Asp Leu Ser Arg Glu Asn Val Leu Ile Thr Gly Gly Gly Arg
 35 40 45

Gly Ile Gly Arg Gln Leu Ala Arg Glu Phe Ala Glu Arg Gly Ala Arg
 50 55 60

Lys Ile Val Leu Trp Gly Arg Thr Glu Lys Cys Leu Lys Glu Thr Thr
 65 70 75 80

Glu Glu Ile Arg Gln Met Gly Thr Glu Cys His Tyr Phe Ile Cys Asp
 85 90 95

Val Gly Asn Arg Glu Glu Val Tyr Gln Thr Ala Lys Ala Val Arg Glu
 100 105 110

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Lys Val Gly Asp Ile Thr Ile Leu Val Asn Asn Ala Ala Val Val His
 115 120 125

Gly Lys Ser Leu Met Asp Ser Asp Asp Asp Ala Leu Leu Lys Ser Gln
 130 135 140

His Ile Asn Thr Leu Gly Gln Phe Trp Thr Thr Lys Ala Phe Leu Pro
 145 150 155 160

Arg Met Leu Glu Leu Gln Asn Gly His Ile Val Cys Leu Asn Ser Val
 165 170 175

Leu Ala Leu Ser Ala Ile Pro Gly Ala Ile Asp Tyr Cys Thr Ser Lys
 180 185 190

Ala Ser Ala Phe Ala Phe Met Glu Ser Leu Thr Leu Gly Leu Leu Asp
 195 200 205

Cys Pro Gly Val Ser Ala Thr Thr Val Leu Pro Phe His Thr Ser Thr
 210 215 220

Glu Met Phe Gln Gly Met Arg Val Arg Phe Pro Asn Leu Phe Pro Pro
 225 230 235 240

Leu Lys Pro Glu Thr Val Ala Arg Arg Thr Val Glu Ala Val Gln Leu
 245 250 255

Asn Gln Ala Leu Leu Leu Leu Pro Trp Thr Met His Ala Leu Val Ile
 260 265 270

Leu Lys Ser Ile Leu Pro Gln Ala Ala Leu Glu Glu Ile His Lys Phe
 275 280 285

Ser Gly Thr Tyr Thr Cys Met Asn Thr Phe Lys Gly Arg Thr
 290 295 300

<210> 100

<211> 674

<212> PRT

<213> Homo sapiens

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<400> 100

Met Pro Ser Tyr Thr Val Thr Val Ala Thr Gly Ser Gln Trp Phe Ala
1 5 10 15

Gly Thr Asp Asp Tyr Ile Tyr Leu Ser Leu Val Gly Ser Ala Gly Cys
20 25 30

Ser Glu Lys His Leu Leu Asp Lys Pro Phe Tyr Asn Asp Phe Glu Arg
35 40 45

Gly Ala Val Asp Ser Tyr Asp Val Thr Val Asp Glu Glu Leu Gly Glu
50 55 60

Ile Gln Leu Val Arg Ile Glu Lys Arg Lys Tyr Trp Leu Asn Asp Asp
65 70 75 80

Trp Tyr Leu Lys Tyr Ile Thr Leu Lys Thr Pro His Gly Asp Tyr Ile
85 90 95

Glu Phe Pro Cys Tyr Arg Trp Ile Thr Gly Asp Val Glu Val Val Leu
100 105 110

Arg Asp Gly Arg Ala Lys Leu Ala Arg Asp Asp Gln Ile His Ile Leu
115 120 125

Lys Gln His Arg Arg Lys Glu Leu Glu Thr Arg Gln Lys Gln Tyr Arg
130 135 140

Trp Met Glu Trp Asn Pro Gly Phe Pro Leu Ser Ile Asp Ala Lys Cys
145 150 155 160

His Lys Asp Leu Pro Arg Asp Ile Gln Phe Asp Ser Glu Lys Gly Val
165 170 175

Asp Phe Val Leu Asn Tyr Ser Lys Ala Met Glu Asn Leu Phe Ile Asn
180 185 190

Arg Phe Met His Met Phe Gln Ser Ser Trp Asn Asp Phe Ala Asp Phe
195 200 205

Glu Lys Ile Phe Val Lys Ile Ser Asn Thr Ile Ser Glu Arg Val Met
210 215 220

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Asn His Trp Gln Glu Asp Leu Met Phe Gly Tyr Gln Phe Leu Asn Gly
 225 230 235 240

Cys Asn Pro Val Leu Ile Arg Arg Cys Thr Glu Leu Pro Glu Lys Leu
 245 250 255

Pro Val Thr Thr Glu Met Val Glu Cys Ser Leu Glu Arg Gln Leu Ser
 260 265 270

Leu Glu Gln Glu Val Gln Gln Gly Asn Ile Phe Ile Val Asp Phe Glu
 275 280 285

Leu Leu Asp Gly Ile Asp Ala Asn Lys Thr Asp Pro Cys Thr Leu Gln
 290 295 300

Phe Leu Ala Ala Pro Ile Cys Leu Leu Tyr Lys Asn Leu Ala Asn Lys
 305 310 315 320

Ile Val Pro Ile Ala Ile Gln Leu Asn Gln Ile Pro Gly Asp Glu Asn
 325 330 335

Pro Ile Phe Leu Pro Ser Asp Ala Lys Tyr Asp Trp Leu Leu Ala Lys
 340 345 350

Ile Trp Val Arg Ser Ser Asp Phe His Val His Gln Thr Ile Thr His
 355 360 365

Leu Leu Arg Thr His Leu Val Ser Glu Val Phe Gly Ile Ala Met Tyr
 370 375 380

Arg Gln Leu Pro Ala Val His Pro Ile Phe Lys Leu Leu Val Ala His
 385 390 395 400

Val Arg Phe Thr Ile Ala Ile Asn Thr Lys Ala Arg Glu Gln Leu Ile
 405 410 415

Cys Glu Cys Gly Leu Phe Asp Lys Ala Asn Ala Thr Gly Gly Gly Gly
 420 425 430

His Val Gln Met Val Gln Arg Ala Met Lys Asp Leu Thr Tyr Ala Ser
 435 440 445

Leu Cys Phe Pro Glu Ala Ile Lys Ala Arg Gly Met Glu Ser Lys Glu
 450 455 460

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Asp Ile Pro Tyr Tyr Phe Tyr Arg Asp Asp Gly Leu Leu Val Trp Glu
 465 470 475 480

Ala Ile Arg Thr Phe Thr Ala Glu Val Val Asp Ile Tyr Tyr Glu Gly
 485 490 495

Asp Gln Val Val Glu Glu Asp Pro Glu Leu Gln Asp Phe Val Asn Asp
 500 505 510

Val Tyr Val Tyr Gly Met Arg Gly Arg Lys Ser Ser Gly Phe Pro Lys
 515 520 525

Ser Val Lys Ser Arg Glu Gln Leu Ser Glu Tyr Leu Thr Val Val Ile
 530 535 540

Phe Thr Ala Ser Ala Gln His Ala Ala Val Asn Phe Gly Gln Tyr Asp
 545 550 555 560

Trp Cys Ser Trp Ile Pro Asn Ala Pro Pro Thr Met Arg Ala Pro Pro
 565 570 575

Pro Thr Ala Lys Gly Val Val Thr Ile Glu Gln Ile Val Asp Thr Leu
 580 585 590

Pro Asp Arg Gly Arg Ser Cys Trp His Leu Gly Ala Val Trp Ala Leu
 595 600 605

Ser Gln Phe Gln Glu Asn Glu Leu Phe Leu Gly Met Tyr Pro Glu Glu
 610 615 620

His Phe Ile Glu Lys Pro Val Lys Glu Ala Met Ala Arg Phe Arg Lys
 625 630 635 640

Asn Leu Glu Ala Ile Val Ser Val Ile Ala Glu Arg Asn Lys Lys Lys
 645 650 655

Gln Leu Pro Tyr Tyr Tyr Leu Ser Pro Asp Arg Ile Pro Asn Ser Val
 660 665 670

Ala Ile

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<210> 101

<211> 299

<212> PRT

<213> Homo sapiens

<400> 101

Met Asp Leu Val Leu Arg Val Ala Asp Tyr Tyr Phe Phe Thr Pro Tyr
 1 5 10 15

Val Tyr Pro Ala Thr Trp Pro Glu Asp Asp Ile Phe Arg Gln Ala Ile
 20 25 30

Ser Leu Leu Ile Val Thr Asn Val Gly Ala Tyr Ile Leu Tyr Phe Phe
 35 40 45

Cys Ala Thr Leu Ser Tyr Tyr Phe Val Phe Asp His Ala Leu Met Lys
 50 55 60

His Pro Gln Phe Leu Lys Asn Gln Val Arg Arg Glu Ile Lys Phe Thr
 65 70 75 80

Val Gln Ala Leu Pro Trp Ile Ser Ile Leu Thr Val Ala Leu Phe Leu
 85 90 95

Leu Glu Ile Arg Gly Tyr Ser Lys Leu His Asp Asp Leu Gly Glu Phe
 100 105 110

Pro Tyr Gly Leu Phe Glu Leu Val Val Ser Ile Ile Ser Phe Leu Phe
 115 120 125

Phe Thr Asp Met Phe Ile Tyr Trp Ile His Arg Gly Leu His His Arg
 130 135 140

Leu Val Tyr Lys Arg Leu His Lys Pro His His Ile Trp Lys Ile Pro
 145 150 155 160

Thr Pro Phe Ala Ser His Ala Phe His Pro Ile Asp Gly Phe Leu Gln
 165 170 175

Ser Leu Pro Tyr His Ile Tyr Pro Phe Ile Phe Pro Leu His Lys Val
 180 185 190

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Val Tyr Leu Ser Leu Tyr Ile Leu Val Asn Ile Trp Thr Ile Ser Ile
195 200 205

His Asp Gly Asp Phe Arg Val Pro Gln Ile Leu Gln Pro Phe Ile Asn
210 215 220

Gly Ser Ala His His Thr Asp His His Met Phe Phe Asp Tyr Asn Tyr
225 230 235 240

Gly Gln Tyr Phe Thr Leu Trp Asp Arg Ile Gly Gly Ser Phe Lys Asn
245 250 255

Pro Ser Ser Phe Glu Gly Lys Gly Pro Leu Ser Tyr Val Lys Glu Met
260 265 270

Thr Glu Gly Lys Arg Ser Ser Pro Ser Gly Asn Gly Cys Lys Asn Glu
275 280 285

Lys Leu Phe Asn Gly Glu Phe Thr Lys Thr Glu
290 295

<210> 102

<211> 676

<212> PRT

<213> Homo sapiens

<400> 102

Met Ala Glu Phe Arg Val Arg Val Ser Thr Gly Glu Ala Phe Gly Ala
1 5 10 15

Gly Thr Trp Asp Lys Val Ser Val Ser Ile Val Gly Thr Arg Gly Glu
20 25 30

Ser Pro Pro Leu Pro Leu Asp Asn Leu Gly Lys Glu Phe Thr Ala Gly
35 40 45

Ala Glu Glu Asp Phe Gln Val Thr Leu Pro Glu Asp Val Gly Arg Val
50 55 60

Leu Leu Leu Arg Val His Lys Ala Pro Pro Val Leu Pro Leu Leu Gly
65 70 75 80

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Pro Leu Ala Pro Asp Ala Trp Phe Cys Arg Trp Phe Gln Leu Thr Pro
 85 90 95

Pro Arg Gly Gly His Leu Leu Phe Pro Cys Tyr Gln Trp Leu Glu Gly
 100 105 110

Ala Gly Thr Leu Val Leu Gln Glu Gly Thr Ala Lys Val Ser Trp Ala
 115 120 125

Asp His His Pro Val Leu Gln Gln Gln Arg Gln Glu Glu Leu Gln Ala
 130 135 140

Arg Gln Glu Met Tyr Gln Trp Lys Ala Tyr Asn Pro Gly Trp Pro His
 145 150 155 160

Cys Leu Asp Glu Lys Thr Val Glu Asp Leu Glu Leu Asn Ile Lys Tyr
 165 170 175

Ser Thr Ala Lys Asn Ala Asn Phe Tyr Leu Gln Ala Gly Ser Ala Phe
 180 185 190

Ala Glu Met Lys Ile Lys Gly Leu Leu Asp Arg Lys Gly Leu Trp Arg
 195 200 205

Ser Leu Asn Glu Met Lys Arg Ile Phe Asn Phe Arg Arg Thr Pro Ala
 210 215 220

Ala Glu His Ala Phe Glu His Trp Gln Glu Asp Ala Phe Phe Ala Ser
 225 230 235 240

Gln Phe Leu Asn Gly Leu Asn Pro Val Leu Ile Arg Arg Cys His Tyr
 245 250 255

Leu Pro Lys Asn Phe Pro Val Thr Asp Ala Met Val Ala Ser Leu Leu
 260 265 270

Gly Pro Gly Thr Ser Leu Gln Ala Glu Leu Glu Lys Gly Ser Leu Phe
 275 280 285

Leu Val Asp His Gly Ile Leu Ser Gly Ile Gln Thr Asn Val Ile Asn
 290 295 300

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Gly Lys Pro Gln Phe Ser Ala Ala Pro Met Thr Leu Leu Tyr Gln Ser
 305 310 315 320

Pro Gly Cys Gly Pro Leu Leu Pro Leu Ala Ile Gln Leu Ser Gln Thr
 325 330 335

Pro Gly Pro Asn Ser Pro Ile Phe Leu Pro Thr Asp Asp Lys Trp Asp
 340 345 350

Trp Leu Leu Ala Lys Thr Trp Val Arg Asn Ala Glu Phe Ser Phe His
 355 360 365

Glu Ala Leu Thr His Leu Leu His Ser His Leu Leu Pro Glu Val Phe
 370 375 380

Thr Leu Ala Thr Leu Arg Gln Leu Pro His Cys His Pro Leu Phe Lys
 385 390 395 400

Leu Leu Ile Pro His Thr Arg Tyr Thr Leu His Ile Asn Thr Leu Ala
 405 410 415

Arg Glu Leu Leu Ile Val Pro Gly Gln Val Val Asp Arg Ser Thr Gly
 420 425 430

Ile Gly Ile Glu Gly Phe Ser Glu Leu Ile Gln Arg Asn Met Lys Gln
 435 440 445

Leu Asn Tyr Ser Leu Leu Cys Leu Pro Glu Asp Ile Arg Thr Arg Gly
 450 455 460

Val Glu Asp Ile Pro Gly Tyr Tyr Tyr Arg Asp Asp Gly Met Gln Ile
 465 470 475 480

Trp Gly Ala Val Glu Arg Phe Val Ser Glu Ile Ile Gly Ile Tyr Tyr
 485 490 495

Pro Ser Asp Glu Ser Val Gln Asp Asp Arg Glu Leu Gln Ala Trp Val
 500 505 510

Arg Glu Ile Phe Ser Lys Gly Phe Leu Asn Gln Glu Ser Ser Gly Ile
 515 520 525

Pro Ser Ser Leu Glu Thr Arg Glu Ala Leu Val Gln Tyr Val Thr Met
 530 535 540

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Val Ile Phe Thr Cys Ser Ala Lys His Ala Ala Val Ser Ala Gly Gln
 545 550 555 560

Phe Asp Ser Cys Ala Trp Met Pro Asn Leu Pro Pro Ser Met Gln Leu
 565 570 575

Pro Pro Pro Thr Ser Lys Gly Leu Ala Thr Cys Glu Gly Phe Ile Ala
 580 585 590

Thr Leu Pro Pro Val Asn Ala Thr Cys Asp Val Ile Leu Ala Leu Trp
 595 600 605

Leu Leu Ser Lys Glu Pro Gly Asp Gln Arg Pro Leu Gly Thr Tyr Pro
 610 615 620

Asp Glu His Phe Thr Glu Glu Ala Pro Arg Arg Ser Ile Ala Thr Phe
 625 630 635 640

Gln Ser Arg Leu Ala Gln Ile Ser Arg Gly Ile Gln Glu Arg Asn Arg
 645 650 655

Gly Leu Val Leu Pro Tyr Thr Tyr Leu Asp Pro Pro Leu Ile Glu Asn
 660 665 670

Ser Val Ser Ile
 675

<210> 103

<211> 311

<212> PRT

<213> Homo sapiens

<400> 103

Arg Thr Arg Gly Ala His Ile Ile Ala Leu Glu Ser Ile Ala Trp Phe
 1 5 10 15

Thr Val Phe Tyr Phe Gly Asn Gly Trp Ile Pro Thr Leu Ile Thr Ala
 20 25 30

Phe Val Leu Ala Thr Ser Gln Ala Gln Ala Gly Trp Leu Gln His Asp
 35 40 45

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Tyr Gly His Leu Ser Val Tyr Arg Lys Pro Lys Trp Asn His Leu Val
 50 55 60

His Lys Phe Val Ile Gly His Leu Lys Gly Ala Ser Ala Asn Trp Trp
 65 70 75 80

Asn His Arg His Phe Gln His His Ala Lys Pro Asn Ile Phe His Lys
 85 90 95

Asp Pro Asp Val Asn Met Leu His Val Phe Val Leu Gly Glu Trp Gln
 100 105 110

Pro Ile Glu Tyr Gly Lys Lys Lys Leu Lys Tyr Leu Pro Tyr Asn His
 115 120 125

Gln His Glu Tyr Phe Phe Leu Ile Gly Pro Pro Leu Leu Ile Pro Met
 130 135 140

Tyr Phe Gln Tyr Gln Ile Ile Met Thr Met Ile Val His Lys Asn Trp
 145 150 155 160

Val Asp Leu Ala Trp Ala Val Ser Tyr Tyr Ile Arg Phe Phe Ile Thr
 165 170 175

Tyr Ile Pro Phe Tyr Gly Ile Leu Gly Ala Leu Leu Phe Leu Asn Phe
 180 185 190

Ile Arg Phe Leu Glu Ser His Trp Phe Val Trp Val Thr Gln Met Asn
 195 200 205

His Ile Val Met Glu Ile Asp Gln Glu Ala Tyr Arg Asp Trp Phe Ser
 210 215 220

Ser Gln Leu Thr Ala Thr Cys Asn Val Glu Gln Ser Phe Phe Asn Asp
 225 230 235 240

Trp Phe Ser Gly His Leu Asn Phe Gln Ile Glu His His Leu Phe Pro
 245 250 255

Thr Met Pro Arg His Asn Leu His Lys Ile Ala Pro Leu Val Lys Ser
 260 265 270

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Leu Cys Ala Lys His Gly Ile Glu Tyr Gln Glu Lys Pro Leu Leu Arg
 275 280 285

Ala Leu Leu Asp Ile Ile Arg Asp Leu Met Lys Ser Gly Lys Leu Trp
 290 295 300

Leu Asp Ala Tyr Leu His Lys
 305 310

<210> 104

<211> 475

<212> PRT

<213> Homo sapiens

<400> 104

Met Ala Ala Lys Leu Gln Pro Asn Ile Pro Lys Ala Lys Ser Leu Asp
 1 5 10 15

Gly Val Thr Asn Asp Arg Thr Ala Ser Gln Gly Gln Trp Gly Arg Ala
 20 25 30

Trp Glu Val Asp Trp Phe Ser Leu Ala Ser Val Ile Phe Leu Leu Leu
 35 40 45

Phe Ala Pro Phe Ile Val Tyr Tyr Phe Ile Met Ala Cys Asp Gln Tyr
 50 55 60

Ser Cys Ala Leu Thr Gly Pro Val Val Asp Ile Val Thr Gly His Ala
 65 70 75 80

Arg Leu Ser Asp Ile Trp Ala Lys Thr Pro Pro Ile Thr Arg Lys Ala
 85 90 95

Ala Gln Leu Tyr Thr Leu Trp Val Thr Phe Gln Val Leu Leu Tyr Thr
 100 105 110

Ser Leu Pro Asp Phe Cys His Lys Phe Leu Pro Gly Tyr Val Gly Gly
 115 120 125

Ile Gln Glu Gly Ala Val Thr Pro Ala Gly Val Val Asn Lys Tyr Gln
 130 135 140

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Ile Asn Gly Leu Gln Ala Trp Leu Leu Thr His Leu Leu Trp Phe Ala
145 150 155 160

Asn Ala His Leu Leu Ser Trp Phe Ser Pro Thr Ile Ile Phe Asp Asn
165 170 175

Trp Ile Pro Leu Leu Trp Cys Ala Asn Ile Leu Gly Tyr Ala Val Ser
180 185 190

Thr Phe Ala Met Val Lys Gly Tyr Phe Phe Pro Thr Ser Ala Arg Asp
195 200 205

Cys Lys Phe Thr Gly Asn Phe Phe Tyr Asn Tyr Met Met Gly Ile Glu
210 215 220

Phe Asn Pro Arg Ile Gly Lys Trp Phe Asp Phe Lys Leu Phe Phe Asn
225 230 235 240

Gly Arg Pro Gly Ile Val Ala Trp Thr Leu Ile Asn Leu Ser Phe Ala
245 250 255

Ala Lys Gln Arg Glu Leu His Ser His Val Thr Asn Ala Met Val Leu
260 265 270

Val Asn Val Leu Gln Ala Ile Tyr Val Ile Asp Phe Phe Trp Asn Glu
275 280 285

Thr Trp Tyr Leu Lys Thr Ile Asp Ile Cys His Asp His Phe Gly Trp
290 295 300

Tyr Leu Gly Trp Gly Asp Cys Val Trp Leu Pro Tyr Leu Tyr Thr Leu
305 310 315 320

Gln Gly Leu Tyr Leu Val Tyr His Pro Val Gln Leu Ser Thr Pro His
325 330 335

Ala Val Gly Val Leu Leu Leu Gly Leu Val Gly Tyr Tyr Ile Phe Arg
340 345 350

Val Ala Asn His Gln Lys Asp Leu Phe Arg Arg Thr Asp Gly Arg Cys
355 360 365

Leu Ile Trp Gly Arg Lys Pro Lys Val Ile Glu Cys Ser Tyr Thr Ser
370 375 380

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Ala Asp Gly Gln Arg His His Ser Lys Leu Leu Val Ser Gly Phe Trp
385 390 395 400

Gly Val Ala Arg His Phe Asn Tyr Val Gly Asp Leu Met Gly Ser Leu
405 410 415

Ala Tyr Cys Leu Ala Cys Gly Gly Gly His Leu Leu Pro Tyr Phe Tyr
420 425 430

Ile Ile Tyr Met Ala Ile Leu Leu Thr His Arg Cys Leu Arg Asp Glu
435 440 445

His Arg Cys Ala Ser Lys Tyr Gly Arg Asp Trp Glu Arg Tyr Thr Ala
450 455 460

Ala Val Pro Tyr Arg Leu Leu Pro Gly Ile Phe
465 470 475

<210> 105

<211> 359

<212> PRT

<213> Homo sapiens

<400> 105

Met Pro Ala His Leu Leu Gln Asp Asp Ile Ser Ser Ser Tyr Thr Thr
1 5 10 15

Thr Thr Thr Ile Thr Ala Pro Pro Pro Gly Val Leu Gln Asn Gly Gly
20 25 30

Asp Lys Leu Glu Thr Met Pro Leu Tyr Leu Glu Asp Asp Ile Arg Pro
35 40 45

Asp Ile Lys Asp Asp Ile Tyr Asp Pro Thr Tyr Lys Asp Lys Glu Gly
50 55 60

Pro Ser Pro Lys Val Glu Tyr Val Trp Arg Asn Ile Ile Leu Met Ser
65 70 75 80

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Leu Leu His Leu Gly Ala Leu Tyr Gly Ile Thr Leu Ile Pro Thr Cys
85 90 95

Lys Phe Tyr Thr Trp Leu Trp Gly Val Phe Tyr Tyr Phe Val Ser Ala
100 105 110

Leu Gly Ile Thr Ala Gly Ala His Arg Leu Trp Ser His Arg Ser Tyr
115 120 125

Lys Ala Arg Leu Pro Leu Arg Leu Phe Leu Ile Ile Ala Asn Thr Met
130 135 140

Ala Phe Gln Asn Asp Val Tyr Glu Trp Ala Arg Asp His Arg Ala His
145 150 155 160

His Lys Phe Ser Glu Thr His Ala Asp Pro His Asn Ser Arg Arg Gly
165 170 175

Phe Phe Phe Ser His Val Gly Trp Leu Leu Val Arg Lys His Pro Ala
180 185 190

Val Lys Glu Lys Gly Ser Thr Leu Asp Leu Ser Asp Leu Glu Ala Glu
195 200 205

Lys Leu Val Met Phe Gln Arg Arg Tyr Tyr Lys Pro Gly Leu Leu Met
210 215 220

Met Cys Phe Ile Leu Pro Thr Leu Val Pro Trp Tyr Phe Trp Gly Glu
225 230 235 240

Thr Phe Gln Asn Ser Val Phe Val Ala Thr Phe Leu Arg Tyr Ala Val
245 250 255

Val Leu Asn Ala Thr Trp Leu Val Asn Ser Ala Ala His Leu Phe Gly
260 265 270

Tyr Arg Pro Tyr Asp Lys Asn Ile Ser Pro Arg Glu Asn Ile Leu Val
275 280 285

Ser Leu Gly Ala Val Gly Glu Gly Phe His Asn Tyr His His Ser Phe
290 295 300

Pro Tyr Asp Tyr Ser Ala Ser Glu Tyr Arg Trp His Ile Asn Phe Asn
305 310 315 320

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Thr Phe Phe Ile Asp Trp Met Ala Ala Leu Gly Leu Thr Tyr Asp Arg
 325 330 335

Lys Lys Val Ser Lys Ala Ala Ile Leu Ala Arg Ile Lys Arg Thr Gly
 340 345 350

Asp Gly Asn Tyr Lys Ser Gly
 355

<210> 106

<211> 339

<212> PRT

<213> Homo sapiens

<400> 106

Met Ala Val Ala Gln Gln Leu Arg Ala Glu Ser Asp Phe Glu Gln Leu
 1 5 10 15

Pro Asp Asp Val Ala Ile Ser Ala Asn Ile Ala Asp Ile Glu Glu Lys
 20 25 30

Arg Gly Phe Thr Ser His Phe Val Phe Val Ile Glu Val Lys Thr Lys
 35 40 45

Gly Gly Ser Lys Tyr Leu Ile Tyr Arg Arg Tyr Arg Gln Phe His Ala
 50 55 60

Leu Gln Ser Lys Leu Glu Glu Arg Phe Gly Pro Asp Ser Lys Ser Ser
 65 70 75 80

Ala Leu Ala Cys Thr Leu Pro Thr Leu Pro Ala Lys Val Tyr Val Gly
 85 90 95

Val Lys Gln Glu Ile Ala Glu Met Arg Ile Pro Ala Leu Asn Ala Tyr
 100 105 110

Met Lys Ser Leu Leu Ser Leu Pro Val Trp Val Leu Met Asp Glu Asp
 115 120 125

Val Arg Ile Phe Phe Tyr Gln Ser Pro Tyr Asp Ser Glu Gln Val Pro
 130 135 140

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Gln Ala Ile Arg Arg Leu Arg Pro Arg Thr Arg Lys Val Lys Ser Val
 145 150 155 160

Ser Pro Gln Gly Asn Ser Val Asp Arg Met Ala Ala Pro Arg Ala Glu
 165 170 175

Ala Leu Phe Asp Phe Thr Gly Asn Ser Lys Leu Glu Leu Asn Phe Lys
 180 185 190

Ala Gly Asp Val Ile Phe Leu Leu Ser Arg Ile Asn Lys Asp Trp Leu
 195 200 205

Glu Gly Thr Val Arg Gly Ala Thr Gly Ile Phe Pro Leu Ser Phe Val
 210 215 220

Lys Ile Leu Lys Asp Phe Pro Glu Glu Asp Asp Pro Thr Asn Trp Leu
 225 230 235 240

Arg Cys Tyr Tyr Tyr Glu Asp Thr Ile Ser Thr Ile Lys Asp Ile Ala
 245 250 255

Val Glu Glu Asp Leu Ser Ser Thr Pro Leu Leu Lys Asp Leu Leu Glu
 260 265 270

Leu Thr Arg Arg Glu Phe Gln Arg Glu Asp Ile Ala Leu Asn Tyr Arg
 275 280 285

Asp Ala Glu Gly Asp Leu Val Arg Leu Leu Ser Asp Glu Asp Val Ala
 290 295 300

Leu Met Val Arg Gln Ala Arg Gly Leu Pro Ser Gln Lys Arg Leu Phe
 305 310 315 320

Pro Trp Lys Leu His Ile Thr Gln Lys Asp Asn Tyr Arg Val Tyr Asn
 325 330 335

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Thr Met Pro

<210> 107

<211> 323

<212> PRT

<213> Homo sapiens

<400> 107

Met	Asp	Ser	Lys	Gln	Gln	Cys	Val	Lys	Leu	Asn	Asp	Gly	His	Phe	Met
1				5					10					15	

Pro	Val	Leu	Gly	Phe	Gly	Thr	Tyr	Ala	Pro	Pro	Glu	Val	Pro	Arg	Ser
			20					25					30		

Lys	Ala	Leu	Glu	Val	Thr	Lys	Leu	Ala	Ile	Glu	Ala	Gly	Phe	Arg	His
		35					40					45			

Ile	Asp	Ser	Ala	His	Leu	Tyr	Asn	Asn	Glu	Glu	Gln	Val	Gly	Leu	Ala
	50					55					60				

Ile	Arg	Ser	Lys	Ile	Ala	Asp	Gly	Ser	Val	Lys	Arg	Glu	Asp	Ile	Phe
65					70					75					80

Tyr	Thr	Ser	Lys	Leu	Trp	Ser	Thr	Phe	His	Arg	Pro	Glu	Leu	Val	Arg
				85					90					95	

Pro	Ala	Leu	Glu	Asn	Ser	Leu	Lys	Lys	Ala	Gln	Leu	Asp	Tyr	Val	Asp
			100					105						110	

Leu	Tyr	Leu	Ile	His	Ser	Pro	Met	Ser	Leu	Lys	Pro	Gly	Glu	Glu	Leu
		115					120					125			

Ser	Pro	Thr	Asp	Glu	Asn	Gly	Lys	Val	Ile	Phe	Asp	Ile	Val	Asp	Leu
	130					135					140				

Cys	Thr	Thr	Trp	Glu	Ala	Met	Glu	Lys	Cys	Lys	Asp	Ala	Gly	Leu	Ala
145					150					155					160

Lys	Ser	Ile	Gly	Val	Ser	Asn	Phe	Asn	Arg	Arg	Gln	Leu	Glu	Met	Ile
				165					170					175	

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Leu Asn Lys Pro Gly Leu Lys Tyr Lys Pro Val Cys Asn Gln Val Glu
 180 185 190

Cys His Pro Tyr Phe Asn Arg Ser Lys Leu Leu Asp Phe Cys Lys Ser
 195 200 205

Lys Asp Ile Val Leu Val Ala Tyr Ser Ala Leu Gly Ser Gln Arg Asp
 210 215 220

Lys Arg Trp Val Asp Pro Asn Ser Pro Val Leu Leu Glu Asp Pro Val
 225 230 235 240

Leu Cys Ala Leu Ala Lys Lys His Lys Arg Thr Pro Ala Leu Ile Ala
 245 250 255

Leu Arg Tyr Gln Leu Gln Arg Gly Val Val Val Leu Ala Lys Ser Tyr
 260 265 270

Asn Glu Gln Arg Ile Arg Gln Asn Val Gln Val Phe Glu Phe Gln Leu
 275 280 285

Thr Ala Glu Asp Met Lys Ala Ile Asp Gly Leu Asp Arg Asn Leu His
 290 295 300

Tyr Phe Asn Ser Asp Ser Phe Ala Ser His Pro Asn Tyr Pro Tyr Ser
 305 310 315 320

Asp Glu Tyr

<210> 108

<211> 588

<212> PRT

<213> Homo sapiens

<400> 108

Met Gly Gly Thr Ala Arg Gly Pro Gly Arg Lys Asp Ala Gly Pro Pro
 1 5 10 15

Gly Ala Gly Leu Pro Pro Gln Gln Arg Arg Leu Gly Asp Gly Val Tyr
 20 25 30

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Asp Thr Phe Met Met Ile Asp Glu Thr Lys Cys Pro Pro Cys Ser Asn
 35 40 45

Val Leu Cys Asn Pro Ser Glu Pro Pro Pro Pro Arg Arg Leu Asn Met
 50 55 60

Thr Thr Glu Gln Phe Thr Gly Asp His Thr Gln His Phe Leu Asp Gly
 65 70 75 80

Gly Glu Met Lys Val Glu Gln Leu Phe Gln Glu Phe Gly Asn Arg Lys
 85 90 95

Ser Asn Thr Ile Gln Ser Asp Gly Ile Ser Asp Ser Glu Lys Cys Ser
 100 105 110

Pro Thr Val Ser Gln Gly Lys Ser Ser Asp Cys Leu Asn Thr Val Lys
 115 120 125

Ser Asn Ser Ser Ser Lys Ala Pro Lys Val Val Pro Leu Thr Pro Glu
 130 135 140

Gln Ala Leu Lys Gln Tyr Lys His His Leu Thr Ala Tyr Glu Lys Leu
 145 150 155 160

Glu Ile Ile Asn Tyr Pro Glu Ile Tyr Phe Val Gly Pro Asn Ala Lys
 165 170 175

Lys Arg His Gly Val Ile Gly Gly Pro Asn Asn Gly Gly Tyr Asp Asp
 180 185 190

Ala Asp Gly Ala Tyr Ile His Val Pro Arg Asp His Leu Ala Tyr Arg
 195 200 205

Tyr Glu Val Leu Lys Ile Ile Gly Lys Gly Ser Phe Gly Gln Val Ala
 210 215 220

Arg Val Tyr Asp His Lys Leu Arg Gln Tyr Val Ala Leu Lys Met Val
 225 230 235 240

Arg Asn Glu Lys Arg Phe His Arg Gln Ala Ala Glu Glu Ile Arg Ile
 245 250 255

Leu Glu His Leu Lys Lys Gln Asp Lys Thr Gly Ser Met Asn Val Ile

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260					265					270					
His	Met	Leu	Glu	Ser	Phe	Thr	Phe	Arg	Asn	His	Val	Cys	Met	Ala	Phe
		275					280					285			
Glu	Leu	Leu	Ser	Ile	Asp	Leu	Tyr	Glu	Leu	Ile	Lys	Lys	Asn	Lys	Phe
	290					295					300				
Gln	Gly	Phe	Ser	Val	Gln	Leu	Val	Arg	Lys	Phe	Ala	Gln	Ser	Ile	Leu
305					310					315					320
Gln	Ser	Leu	Asp	Ala	Leu	His	Lys	Asn	Lys	Ile	Ile	His	Cys	Asp	Leu
				325					330					335	
Lys	Pro	Glu	Asn	Ile	Leu	Leu	Lys	His	His	Gly	Arg	Ser	Ser	Thr	Lys
			340					345					350		
Val	Ile	Asp	Phe	Gly	Ser	Ser	Cys	Phe	Glu	Tyr	Gln	Lys	Leu	Tyr	Thr
		355					360					365			
Tyr	Ile	Gln	Ser	Arg	Phe	Tyr	Arg	Ala	Pro	Glu	Ile	Ile	Leu	Gly	Ser
	370					375					380				
Arg	Tyr	Ser	Thr	Pro	Ile	Asp	Ile	Trp	Ser	Phe	Arg	Cys	Ile	Leu	Ala
385					390					395					400
Glu	Leu	Leu	Thr	Gly	Gln	Pro	Leu	Phe	Pro	Gly	Glu	Asp	Glu	Gly	Asp
				405					410					415	
Gln	Leu	Ala	Cys	Met	Met	Glu	Leu	Leu	Gly	Met	Pro	Pro	Pro	Lys	Leu
			420					425					430		
Leu	Glu	Gln	Ser	Lys	Arg	Ala	Lys	Tyr	Phe	Ile	Asn	Ser	Lys	Gly	Ile
		435					440					445			
Pro	Arg	Tyr	Cys	Ser	Val	Thr	Thr	Gln	Ala	Asp	Gly	Arg	Val	Val	Leu
	450					455					460				
Val	Gly	Gly	Arg	Ser	Arg	Arg	Gly	Lys	Lys	Arg	Gly	Pro	Pro	Gly	Ser
465					470					475					480
Lys	Asp	Trp	Gly	Thr	Ala	Leu	Lys	Gly	Cys	Asp	Asp	Tyr	Leu	Phe	Ile
				485					490					495	

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Glu Phe Leu Lys Arg Cys Leu His Trp Asp Pro Ser Ala Arg Leu Thr
 500 505 510

Pro Ala Gln Ala Leu Arg His Pro Trp Ile Ser Lys Ser Val Pro Arg
 515 520 525

Pro Leu Thr Thr Ile Asp Lys Val Ser Gly Lys Arg Val Val Asn Pro
 530 535 540

Ala Ser Ala Phe Gln Gly Leu Gly Ser Lys Leu Pro Pro Val Val Gly
 545 550 555 560

Ile Ala Asn Lys Leu Lys Ala Asn Leu Met Ser Glu Thr Asn Gly Ser
 565 570 575

Ile Pro Leu Cys Ser Val Leu Pro Lys Leu Ile Ser
 580 585

<210> 109

<211> 365

<212> PRT

<213> Homo sapiens

<400> 109

Met Ser Leu Ile Arg Lys Lys Gly Phe Tyr Lys Gln Glu Leu Asn Lys
 1 5 10 15

Thr Ala Trp Glu Leu Pro Lys Thr Tyr Val Ser Pro Thr His Val Gly
 20 25 30

Ser Gly Ala Tyr Gly Ser Trp Cys Ser Ala Ile Asp Lys Arg Ser Gly
 35 40 45

Glu Lys Val Ala Ile Lys Lys Leu Ser Arg Pro Phe Gln Ser Glu Ile
 50 55 60

Phe Ala Lys Arg Ala Tyr Arg Glu Leu Leu Leu Leu Lys His Met Gln
 65 70 75 80

His Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Ser Ser
 85 90 95

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Leu Arg Asn Phe Tyr Asp Phe Tyr Leu Val Met Pro Phe Met Gln Thr
 100 105 110

Asp Leu Gln Lys Ile Met Gly Met Glu Phe Ser Glu Glu Lys Ile Gln
 115 120 125

Tyr Leu Val Tyr Gln Met Leu Lys Gly Leu Lys Tyr Ile His Ser Ala
 130 135 140

Gly Val Val His Arg Asp Leu Lys Pro Gly Asn Leu Ala Val Asn Glu
 145 150 155 160

Asp Cys Glu Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg His Ala Asp
 165 170 175

Ala Glu Met Thr Gly Tyr Val Val Thr Arg Trp Tyr Arg Ala Pro Glu
 180 185 190

Val Ile Leu Ser Trp Met His Tyr Asn Gln Thr Val Asp Ile Trp Ser
 195 200 205

Val Gly Cys Ile Met Ala Glu Met Leu Thr Gly Lys Thr Leu Phe Lys
 210 215 220

Gly Lys Asp Tyr Leu Asp Gln Leu Thr Gln Ile Leu Lys Val Thr Gly
 225 230 235 240

Val Pro Gly Thr Glu Phe Val Gln Lys Leu Asn Asp Lys Ala Ala Lys
 245 250 255

Ser Tyr Ile Gln Ser Leu Pro Gln Thr Pro Arg Lys Asp Phe Thr Gln
 260 265 270

Leu Phe Pro Arg Ala Ser Pro Gln Ala Ala Asp Leu Leu Glu Lys Met
 275 280 285

Leu Glu Leu Asp Val Asp Lys Arg Leu Thr Ala Ala Gln Ala Leu Thr
 290 295 300

His Pro Phe Phe Glu Pro Phe Arg Asp Pro Glu Glu Glu Thr Glu Ala
 305 310 315 320

Gln Gln Pro Phe Asp Asp Ser Leu Glu His Glu Lys Leu Thr Val Asp
 325 330 335

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Glu Trp Lys Gln His Ile Tyr Lys Glu Ile Val Asn Phe Ser Pro Ile
 340 345 350

Ala Arg Lys Asp Ser Arg Arg Arg Ser Gly Met Lys Leu
 355 360 365

<210> 110

<211> 379

<212> PRT

<213> Homo sapiens

<400> 110

Met Ala Ala Ala Ala Ala Gln Gly Gly Gly Gly Gly Glu Pro Arg Arg
 1 5 10 15

Thr Glu Gly Val Gly Pro Gly Val Pro Gly Glu Val Glu Met Val Lys
 20 25 30

Gly Gln Pro Phe Asp Val Gly Pro Arg Tyr Thr Gln Leu Gln Tyr Ile
 35 40 45

Gly Glu Gly Ala Tyr Gly Met Val Ser Ser Ala Tyr Asp His Val Arg
 50 55 60

Lys Thr Arg Val Ala Ile Lys Lys Ile Ser Pro Phe Glu His Gln Thr
 65 70 75 80

Tyr Cys Gln Arg Thr Leu Arg Glu Ile Gln Ile Leu Leu Arg Phe Arg
 85 90 95

His Glu Asn Val Ile Gly Ile Arg Asp Ile Leu Arg Ala Ser Thr Leu
 100 105 110

Glu Ala Met Arg Asp Val Tyr Ile Val Gln Asp Leu Met Glu Thr Asp
 115 120 125

Leu Tyr Lys Leu Leu Lys Ser Gln Gln Leu Ser Asn Asp His Ile Cys
 130 135 140

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Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala
 145 150 155 160

Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu Leu Ser Asn Thr
 165 170 175

Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala Arg Ile Ala Asp
 180 185 190

Pro Glu His Asp His Thr Gly Phe Leu Thr Glu Tyr Val Ala Thr Arg
 195 200 205

Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys Gly Tyr Thr Lys
 210 215 220

Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala Glu Met Leu Ser
 225 230 235 240

Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp Gln Leu Asn His
 245 250 255

Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp Leu Asn Cys Ile
 260 265 270

Ile Asn Met Lys Ala Arg Asn Tyr Leu Gln Ser Leu Pro Ser Lys Thr
 275 280 285

Lys Val Ala Trp Ala Lys Leu Phe Pro Lys Ser Asp Ser Lys Ala Leu
 290 295 300

Asp Leu Leu Asp Arg Met Leu Thr Phe Asn Pro Asn Lys Arg Ile Thr
 305 310 315 320

Val Glu Glu Ala Leu Ala His Pro Tyr Leu Glu Gln Tyr Tyr Asp Pro
 325 330 335

Thr Asp Glu Pro Val Ala Glu Glu Pro Phe Thr Phe Ala Met Glu Leu
 340 345 350

Asp Asp Leu Pro Lys Glu Arg Leu Lys Glu Leu Ile Phe Gln Glu Thr
 355 360 365

Ala Arg Phe Gln Pro Gly Val Leu Glu Ala Pro
 370 375

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<210> 111

<211> 847

<212> PRT

<213> Homo sapiens

<400> 111

Met Glu Pro Leu Lys Ser Leu Phe Leu Lys Ser Pro Leu Gly Ser Trp
 1 5 10 15

Asn Gly Ser Gly Ser Gly Gly Gly Gly Gly Gly Gly Gly Arg Pro
 20 25 30

Glu Gly Ser Pro Lys Ala Ala Gly Tyr Ala Asn Pro Val Trp Thr Ala
 35 40 45

Leu Phe Asp Tyr Glu Pro Ser Gly Gln Asp Glu Leu Ala Leu Arg Lys
 50 55 60

Gly Asp Arg Val Glu Val Leu Ser Arg Asp Ala Ala Ile Ser Gly Asp
 65 70 75 80

Glu Gly Trp Trp Ala Gly Gln Val Gly Gly Gln Val Gly Ile Phe Pro
 85 90 95

Ser Asn Tyr Val Ser Arg Gly Gly Gly Pro Pro Pro Cys Glu Val Ala
 100 105 110

Ser Phe Gln Glu Leu Arg Leu Glu Glu Val Ile Gly Ile Gly Gly Phe
 115 120 125

Gly Lys Val Tyr Arg Gly Ser Trp Arg Gly Glu Leu Val Ala Val Lys
 130 135 140

Ala Ala Arg Gln Asp Pro Asp Glu Asp Ile Ser Val Thr Ala Glu Ser
 145 150 155 160

Val Arg Gln Glu Ala Arg Leu Phe Ala Met Leu Ala His Pro Asn Ile
 165 170 175

Ile Ala Leu Lys Ala Val Cys Leu Glu Glu Pro Asn Leu Cys Leu Val
 180 185 190

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Met Glu Tyr Ala Ala Gly Gly Pro Leu Ser Arg Ala Leu Ala Gly Arg
 195 200 205

Arg Val Pro Pro His Val Leu Val Asn Trp Ala Val Gln Ile Ala Arg
 210 215 220

Gly Met His Tyr Leu His Cys Glu Ala Leu Val Pro Val Ile His Arg
 225 230 235 240

Asp Leu Lys Ser Asn Asn Ile Leu Leu Leu Gln Pro Ile Glu Ser Asp
 245 250 255

Asp Met Glu His Lys Thr Leu Lys Ile Thr Asp Phe Gly Leu Ala Arg
 260 265 270

Glu Trp His Lys Thr Thr Gln Met Ser Ala Ala Gly Thr Tyr Ala Trp
 275 280 285

Met Ala Pro Glu Val Ile Lys Ala Ser Thr Phe Ser Lys Gly Ser Asp
 290 295 300

Val Trp Ser Phe Gly Val Leu Leu Trp Glu Leu Leu Thr Gly Glu Val
 305 310 315 320

Pro Tyr Arg Gly Ile Asp Cys Leu Ala Val Ala Tyr Gly Val Ala Val
 325 330 335

Asn Lys Leu Thr Leu Pro Ile Pro Ser Thr Cys Pro Glu Pro Phe Ala
 340 345 350

Gln Leu Met Ala Asp Cys Trp Ala Gln Asp Pro His Arg Arg Pro Asp
 355 360 365

Phe Ala Ser Ile Leu Gln Gln Leu Glu Ala Leu Glu Ala Gln Val Leu
 370 375 380

Arg Glu Met Pro Arg Asp Ser Phe His Ser Met Gln Glu Gly Trp Lys
 385 390 395 400

Arg Glu Ile Gln Gly Leu Phe Asp Glu Leu Arg Ala Lys Glu Lys Glu
 405 410 415

Leu Leu Ser Arg Glu Glu Glu Leu Thr Arg Ala Ala Arg Glu Gln Arg

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420	425	430
Ser Gln Ala Glu Gln Leu Arg Arg Arg Glu His Leu Leu Ala Gln Trp		
435	440	445
Glu Leu Glu Val Phe Glu Arg Glu Leu Thr Leu Leu Leu Gln Gln Val		
450	455	460
Asp Arg Glu Arg Pro His Val Arg Arg Arg Arg Gly Thr Phe Lys Arg		
465	470	475
Ser Lys Leu Arg Ala Arg Asp Gly Gly Glu Arg Ile Ser Met Pro Leu		
485	490	495
Asp Phe Lys His Arg Ile Thr Val Gln Ala Ser Pro Gly Leu Asp Arg		
500	505	510
Arg Arg Asn Val Phe Glu Val Gly Pro Gly Asp Ser Pro Thr Phe Pro		
515	520	525
Arg Phe Arg Ala Ile Gln Leu Glu Pro Ala Glu Pro Gly Gln Ala Trp		
530	535	540
Gly Arg Gln Ser Pro Arg Arg Leu Glu Asp Ser Ser Asn Gly Glu Arg		
545	550	555
Arg Ala Cys Trp Ala Trp Gly Pro Ser Ser Pro Lys Pro Gly Glu Ala		
565	570	575
Gln Asn Gly Arg Arg Arg Ser Arg Met Asp Glu Ala Thr Trp Tyr Leu		
580	585	590
Asp Ser Asp Asp Ser Ser Pro Leu Gly Ser Pro Ser Thr Pro Pro Ala		
595	600	605
Leu Asn Gly Asn Pro Pro Arg Pro Ser Leu Glu Pro Glu Glu Pro Lys		
610	615	620
Arg Pro Val Pro Ala Glu Arg Gly Ser Ser Ser Gly Thr Pro Lys Leu		
625	630	635
Ile Gln Arg Ala Leu Leu Arg Gly Thr Ala Leu Leu Ala Ser Leu Gly		
645	650	655

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Leu Gly Arg Asp Leu Gln Pro Pro Gly Gly Pro Gly Arg Glu Arg Gly
660 665 670

Glu Ser Pro Thr Thr Pro Pro Thr Pro Thr Pro Ala Pro Cys Pro Thr
675 680 685

Glu Pro Pro Pro Ser Pro Leu Ile Cys Phe Ser Leu Lys Thr Pro Asp
690 695 700

Ser Pro Pro Thr Pro Ala Pro Leu Leu Leu Asp Leu Gly Ile Pro Val
705 710 715 720

Gly Gln Arg Ser Ala Lys Ser Pro Arg Arg Glu Glu Glu Pro Arg Gly
725 730 735

Gly Thr Val Ser Pro Pro Pro Gly Thr Ser Arg Ser Ala Pro Gly Thr
740 745 750

Pro Gly Thr Pro Arg Ser Pro Pro Leu Gly Leu Ile Ser Arg Pro Arg
755 760 765

Pro Ser Pro Leu Arg Ser Arg Ile Asp Pro Trp Ser Phe Val Ser Ala
770 775 780

Gly Pro Arg Pro Ser Pro Leu Pro Ser Pro Gln Pro Ala Pro Arg Arg
785 790 795 800

Ala Pro Trp Thr Leu Phe Pro Asp Ser Asp Pro Phe Trp Asp Ser Pro
805 810 815

Pro Ala Asn Pro Phe Gln Gly Gly Pro Gln Asp Cys Arg Ala Gln Thr
820 825 830

Lys Asp Met Gly Ala Gln Ala Pro Trp Val Pro Glu Ala Gly Pro
835 840 845

<210> 112

<211> 4544

<212> PRT

<213> Homo sapiens

<400> 112

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Met Leu Thr Pro Pro Leu Leu Leu Leu Leu Pro Leu Leu Ser Ala Leu
1 5 10 15

Val Ala Ala Ala Ile Asp Ala Pro Lys Thr Cys Ser Pro Lys Gln Phe
20 25 30

Ala Cys Arg Asp Gln Ile Thr Cys Ile Ser Lys Gly Trp Arg Cys Asp
35 40 45

Gly Glu Arg Asp Cys Pro Asp Gly Ser Asp Glu Ala Pro Glu Ile Cys
50 55 60

Pro Gln Ser Lys Ala Gln Arg Cys Gln Pro Asn Glu His Asn Cys Leu
65 70 75 80

Gly Thr Glu Leu Cys Val Pro Met Ser Arg Leu Cys Asn Gly Val Gln
85 90 95

Asp Cys Met Asp Gly Ser Asp Glu Gly Pro His Cys Arg Glu Leu Gln
100 105 110

Gly Asn Cys Ser Arg Leu Gly Cys Gln His His Cys Val Pro Thr Leu
115 120 125

Asp Gly Pro Thr Cys Tyr Cys Asn Ser Ser Phe Gln Leu Gln Ala Asp
130 135 140

Gly Lys Thr Cys Lys Asp Phe Asp Glu Cys Ser Val Tyr Gly Thr Cys
145 150 155 160

Ser Gln Leu Cys Thr Asn Thr Asp Gly Ser Phe Ile Cys Gly Cys Val
165 170 175

Glu Gly Tyr Leu Leu Gln Pro Asp Asn Arg Ser Cys Lys Ala Lys Asn
180 185 190

Glu Pro Val Asp Arg Pro Pro Val Leu Leu Ile Ala Asn Ser Gln Asn
195 200 205

Ile Leu Ala Thr Tyr Leu Ser Gly Ala Gln Val Ser Thr Ile Thr Pro
210 215 220

Thr Ser Thr Arg Gln Thr Thr Ala Met Asp Phe Ser Tyr Ala Asn Glu
225 230 235 240

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Thr Val Cys Trp Val His Val Gly Asp Ser Ala Ala Gln Thr Gln Leu
245 250 255

Lys Cys Ala Arg Met Pro Gly Leu Lys Gly Phe Val Asp Glu His Thr
260 265 270

Ile Asn Ile Ser Leu Ser Leu His His Val Glu Gln Met Ala Ile Asp
275 280 285

Trp Leu Thr Gly Asn Phe Tyr Phe Val Asp Asp Ile Asp Asp Arg Ile
290 295 300

Phe Val Cys Asn Arg Asn Gly Asp Thr Cys Val Thr Leu Leu Asp Leu
305 310 315 320

Glu Leu Tyr Asn Pro Lys Gly Ile Ala Leu Asp Pro Ala Met Gly Lys
325 330 335

Val Phe Phe Thr Asp Tyr Gly Gln Ile Pro Lys Val Glu Arg Cys Asp
340 345 350

Met Asp Gly Gln Asn Arg Thr Lys Leu Val Asp Ser Lys Ile Val Phe
355 360 365

Pro His Gly Ile Thr Leu Asp Leu Val Ser Arg Leu Val Tyr Trp Ala
370 375 380

Asp Ala Tyr Leu Asp Tyr Ile Glu Val Val Asp Tyr Glu Gly Lys Gly
385 390 395 400

Arg Gln Thr Ile Ile Gln Gly Ile Leu Ile Glu His Leu Tyr Gly Leu
405 410 415

Thr Val Phe Glu Asn Tyr Leu Tyr Ala Thr Asn Ser Asp Asn Ala Asn
420 425 430

Ala Gln Gln Lys Thr Ser Val Ile Arg Val Asn Arg Phe Asn Ser Thr
435 440 445

Glu Tyr Gln Val Val Thr Arg Val Asp Lys Gly Gly Ala Leu His Ile
450 455 460

Tyr His Gln Arg Arg Gln Pro Arg Val Arg Ser His Ala Cys Glu Asn

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465		470		475		480
Asp Gln Tyr Gly Lys Pro Gly Gly Cys Ser Asp Ile Cys Leu Leu Ala	485		490		495	
Asn Ser His Lys Ala Arg Thr Cys Arg Cys Arg Ser Gly Phe Ser Leu	500		505		510	
Gly Ser Asp Gly Lys Ser Cys Lys Lys Pro Glu His Glu Leu Phe Leu	515		520		525	
Val Tyr Gly Lys Gly Arg Pro Gly Ile Ile Arg Gly Met Asp Met Gly	530		535		540	
Ala Lys Val Pro Asp Glu His Met Ile Pro Ile Glu Asn Leu Met Asn	545		550		555	560
Pro Arg Ala Leu Asp Phe His Ala Glu Thr Gly Phe Ile Tyr Phe Ala	565		570		575	
Asp Thr Thr Ser Tyr Leu Ile Gly Arg Gln Lys Ile Asp Gly Thr Glu	580		585		590	
Arg Glu Thr Ile Leu Lys Asp Gly Ile His Asn Val Glu Gly Val Ala	595		600		605	
Val Asp Trp Met Gly Asp Asn Leu Tyr Trp Thr Asp Asp Gly Pro Lys	610		615		620	
Lys Thr Ile Ser Val Ala Arg Leu Glu Lys Ala Ala Gln Thr Arg Lys	625		630		635	640
Thr Leu Ile Glu Gly Lys Met Thr His Pro Arg Ala Ile Val Val Asp	645		650		655	
Pro Leu Asn Gly Trp Met Tyr Trp Thr Asp Trp Glu Glu Asp Pro Lys	660		665		670	
Asp Ser Arg Arg Gly Arg Leu Glu Arg Ala Trp Met Asp Gly Ser His	675		680		685	
Arg Asp Ile Phe Val Thr Ser Lys Thr Val Leu Trp Pro Asn Gly Leu	690		695		700	

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Ser Leu Asp Ile Pro Ala Gly Arg Leu Tyr Trp Val Asp Ala Phe Tyr
705 710 715 720

Asp Arg Ile Glu Thr Ile Leu Leu Asn Gly Thr Asp Arg Lys Ile Val
725 730 735

Tyr Glu Gly Pro Glu Leu Asn His Ala Phe Gly Leu Cys His His Gly
740 745 750

Asn Tyr Leu Phe Trp Thr Glu Tyr Arg Ser Gly Ser Val Tyr Arg Leu
755 760 765

Glu Arg Gly Val Gly Gly Ala Pro Pro Thr Val Thr Leu Leu Arg Ser
770 775 780

Glu Arg Pro Pro Ile Phe Glu Ile Arg Met Tyr Asp Ala Gln Gln Gln
785 790 795 800

Gln Val Gly Thr Asn Lys Cys Arg Val Asn Asn Gly Gly Cys Ser Ser
805 810 815

Leu Cys Leu Ala Thr Pro Gly Ser Arg Gln Cys Ala Cys Ala Glu Asp
820 825 830

Gln Val Leu Asp Ala Asp Gly Val Thr Cys Leu Ala Asn Pro Ser Tyr
835 840 845

Val Pro Pro Pro Gln Cys Gln Pro Gly Glu Phe Ala Cys Ala Asn Ser
850 855 860

Arg Cys Ile Gln Glu Arg Trp Lys Cys Asp Gly Asp Asn Asp Cys Leu
865 870 875 880

Asp Asn Ser Asp Glu Ala Pro Ala Leu Cys His Gln His Thr Cys Pro
885 890 895

Ser Asp Arg Phe Lys Cys Glu Asn Asn Arg Cys Ile Pro Asn Arg Trp
900 905 910

Leu Cys Asp Gly Asp Asn Asp Cys Gly Asn Ser Glu Asp Glu Ser Asn
915 920 925

Ala Thr Cys Ser Ala Arg Thr Cys Pro Pro Asn Gln Phe Ser Cys Ala
930 935 940

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Ser Gly Arg Cys Ile Pro Ile Ser Trp Thr Cys Asp Leu Asp Asp Asp
 945 950 955 960

Cys Gly Asp Arg Ser Asp Glu Ser Ala Ser Cys Ala Tyr Pro Thr Cys
 965 970 975

Phe Pro Leu Thr Gln Phe Thr Cys Asn Asn Gly Arg Cys Ile Asn Ile
 980 985 990

Asn Trp Arg Cys Asp Asn Asp Asn Asp Cys Gly Asp Asn Ser Asp Glu
 995 1000 1005

Ala Gly Cys Ser His Ser Cys Ser Ser Thr Gln Phe Lys Cys Asn
 1010 1015 1020

Ser Gly Arg Cys Ile Pro Glu His Trp Thr Cys Asp Gly Asp Asn
 1025 1030 1035

Asp Cys Gly Asp Tyr Ser Asp Glu Thr His Ala Asn Cys Thr Asn
 1040 1045 1050

Gln Ala Thr Arg Pro Pro Gly Gly Cys His Thr Asp Glu Phe Gln
 1055 1060 1065

Cys Arg Leu Asp Gly Leu Cys Ile Pro Leu Arg Trp Arg Cys Asp
 1070 1075 1080

Gly Asp Thr Asp Cys Met Asp Ser Ser Asp Glu Lys Ser Cys Glu
 1085 1090 1095

Gly Val Thr His Val Cys Asp Pro Ser Val Lys Phe Gly Cys Lys
 1100 1105 1110

Asp Ser Ala Arg Cys Ile Ser Lys Ala Trp Val Cys Asp Gly Asp
 1115 1120 1125

Asn Asp Cys Glu Asp Asn Ser Asp Glu Glu Asn Cys Glu Ser Leu
 1130 1135 1140

Ala Cys Arg Pro Pro Ser His Pro Cys Ala Asn Asn Thr Ser Val
 1145 1150 1155

Cys Leu Pro Pro Asp Lys Leu Cys Asp Gly Asn Asp Asp Cys Gly
 1160 1165 1170

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Asp Gly 1175	Ser Asp Glu Gly Glu 1180	Leu Cys Asp Gln Cys 1185	Ser Leu Asn
Asn Gly 1190	Gly Cys Ser His Asn 1195	Cys Ser Val Ala Pro 1200	Gly Glu Gly
Ile Val 1205	Cys Ser Cys Pro Leu 1210	Gly Met Glu Leu Gly 1215	Pro Asp Asn
His Thr 1220	Cys Gln Ile Gln Ser 1225	Tyr Cys Ala Lys His 1230	Leu Lys Cys
Ser Gln 1235	Lys Cys Asp Gln Asn 1240	Lys Phe Ser Val Lys 1245	Cys Ser Cys
Tyr Glu 1250	Gly Trp Val Leu Glu 1255	Pro Asp Gly Glu Ser 1260	Cys Arg Ser
Leu Asp 1265	Pro Phe Lys Pro Phe 1270	Ile Ile Phe Ser Asn 1275	Arg His Glu
Ile Arg 1280	Arg Ile Asp Leu His 1285	Lys Gly Asp Tyr Ser 1290	Val Leu Val
Pro Gly 1295	Leu Arg Asn Thr Ile 1300	Ala Leu Asp Phe His 1305	Leu Ser Gln
Ser Ala 1310	Leu Tyr Trp Thr Asp 1315	Val Val Glu Asp Lys 1320	Ile Tyr Arg
Gly Lys 1325	Leu Leu Asp Asn Gly 1330	Ala Leu Thr Ser Phe 1335	Glu Val Val
Ile Gln 1340	Tyr Gly Leu Ala Thr 1345	Pro Glu Gly Leu Ala 1350	Val Asp Trp
Ile Ala 1355	Gly Asn Ile Tyr Trp 1360	Val Glu Ser Asn Leu 1365	Asp Gln Ile
Glu Val 1370	Ala Lys Leu Asp Gly 1375	Thr Leu Arg Thr Thr 1380	Leu Leu Ala

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Gly	Asp	Ile	Glu	His	Pro	Arg	Ala	Ile	Ala	Leu	Asp	Pro	Arg	Asp
1385						1390					1395			
Gly	Ile	Leu	Phe	Trp	Thr	Asp	Trp	Asp	Ala	Ser	Leu	Pro	Arg	Ile
1400						1405					1410			
Glu	Ala	Ala	Ser	Met	Ser	Gly	Ala	Gly	Arg	Arg	Thr	Val	His	Arg
1415						1420					1425			
Glu	Thr	Gly	Ser	Gly	Gly	Trp	Pro	Asn	Gly	Leu	Thr	Val	Asp	Tyr
1430						1435					1440			
Leu	Glu	Lys	Arg	Ile	Leu	Trp	Ile	Asp	Ala	Arg	Ser	Asp	Ala	Ile
1445						1450					1455			
Tyr	Ser	Ala	Arg	Tyr	Asp	Gly	Ser	Gly	His	Met	Glu	Val	Leu	Arg
1460						1465					1470			
Gly	His	Glu	Phe	Leu	Ser	His	Pro	Phe	Ala	Val	Thr	Leu	Tyr	Gly
1475						1480					1485			
Gly	Glu	Val	Tyr	Trp	Thr	Asp	Trp	Arg	Thr	Asn	Thr	Leu	Ala	Lys
1490						1495					1500			
Ala	Asn	Lys	Trp	Thr	Gly	His	Asn	Val	Thr	Val	Val	Gln	Arg	Thr
1505						1510					1515			
Asn	Thr	Gln	Pro	Phe	Asp	Leu	Gln	Val	Tyr	His	Pro	Ser	Arg	Gln
1520						1525					1530			
Pro	Met	Ala	Pro	Asn	Pro	Cys	Glu	Ala	Asn	Gly	Gly	Gln	Gly	Pro
1535						1540					1545			
Cys	Ser	His	Leu	Cys	Leu	Ile	Asn	Tyr	Asn	Arg	Thr	Val	Ser	Cys
1550						1555					1560			
Ala	Cys	Pro	His	Leu	Met	Lys	Leu	His	Lys	Asp	Asn	Thr	Thr	Cys
1565						1570					1575			
Tyr	Glu	Phe	Lys	Lys	Phe	Leu	Leu	Tyr	Ala	Arg	Gln	Met	Glu	Ile
1580						1585					1590			
Arg	Gly	Val	Asp	Leu	Asp	Ala	Pro	Tyr	Tyr	Asn	Tyr	Ile	Ile	Ser
1595						1600					1605			

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Phe	Thr	Val	Pro	Asp	Ile	Asp	Asn	Val	Thr	Val	Leu	Asp	Tyr	Asp
1610						1615					1620			
Ala	Arg	Glu	Gln	Arg	Val	Tyr	Trp	Ser	Asp	Val	Arg	Thr	Gln	Ala
1625						1630					1635			
Ile	Lys	Arg	Ala	Phe	Ile	Asn	Gly	Thr	Gly	Val	Glu	Thr	Val	Val
1640						1645					1650			
Ser	Ala	Asp	Leu	Pro	Asn	Ala	His	Gly	Leu	Ala	Val	Asp	Trp	Val
1655						1660					1665			
Ser	Arg	Asn	Leu	Phe	Trp	Thr	Ser	Tyr	Asp	Thr	Asn	Lys	Lys	Gln
1670						1675					1680			
Ile	Asn	Val	Ala	Arg	Leu	Asp	Gly	Ser	Phe	Lys	Asn	Ala	Val	Val
1685						1690					1695			
Gln	Gly	Leu	Glu	Gln	Pro	His	Gly	Leu	Val	Val	His	Pro	Leu	Arg
1700						1705					1710			
Gly	Lys	Leu	Tyr	Trp	Thr	Asp	Gly	Asp	Asn	Ile	Ser	Met	Ala	Asn
1715						1720					1725			
Met	Asp	Gly	Ser	Asn	Arg	Thr	Leu	Leu	Phe	Ser	Gly	Gln	Lys	Gly
1730						1735					1740			
Pro	Val	Gly	Leu	Ala	Ile	Asp	Phe	Pro	Glu	Ser	Lys	Leu	Tyr	Trp
1745						1750					1755			
Ile	Ser	Ser	Gly	Asn	His	Thr	Ile	Asn	Arg	Cys	Asn	Leu	Asp	Gly
1760						1765					1770			
Ser	Gly	Leu	Glu	Val	Ile	Asp	Ala	Met	Arg	Ser	Gln	Leu	Gly	Lys
1775						1780					1785			
Ala	Thr	Ala	Leu	Ala	Ile	Met	Gly	Asp	Lys	Leu	Trp	Trp	Ala	Asp
1790						1795					1800			
Gln	Val	Ser	Glu	Lys	Met	Gly	Thr	Cys	Ser	Lys	Ala	Asp	Gly	Ser
1805						1810					1815			
Gly	Ser	Val	Val	Leu	Arg	Asn	Ser	Thr	Thr	Leu	Val	Met	His	Met
1820						1825					1830			

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Lys	Val	Tyr	Asp	Glu	Ser	Ile	Gln	Leu	Asp	His	Lys	Gly	Thr	Asn
1835						1840					1845			
Pro	Cys	Ser	Val	Asn	Asn	Gly	Asp	Cys	Ser	Gln	Leu	Cys	Leu	Pro
1850						1855					1860			
Thr	Ser	Glu	Thr	Thr	Arg	Ser	Cys	Met	Cys	Thr	Ala	Gly	Tyr	Ser
1865						1870					1875			
Leu	Arg	Ser	Gly	Gln	Gln	Ala	Cys	Glu	Gly	Val	Gly	Ser	Phe	Leu
1880						1885					1890			
Leu	Tyr	Ser	Val	His	Glu	Gly	Ile	Arg	Gly	Ile	Pro	Leu	Asp	Pro
1895						1900					1905			
Asn	Asp	Lys	Ser	Asp	Ala	Leu	Val	Pro	Val	Ser	Gly	Thr	Ser	Leu
1910						1915					1920			
Ala	Val	Gly	Ile	Asp	Phe	His	Ala	Glu	Asn	Asp	Thr	Ile	Tyr	Trp
1925						1930					1935			
Val	Asp	Met	Gly	Leu	Ser	Thr	Ile	Ser	Arg	Ala	Lys	Arg	Asp	Gln
1940						1945					1950			
Thr	Trp	Arg	Glu	Asp	Val	Val	Thr	Asn	Gly	Ile	Gly	Arg	Val	Glu
1955						1960					1965			
Gly	Ile	Ala	Val	Asp	Trp	Ile	Ala	Gly	Asn	Ile	Tyr	Trp	Thr	Asp
1970						1975					1980			
Gln	Gly	Phe	Asp	Val	Ile	Glu	Val	Ala	Arg	Leu	Asn	Gly	Ser	Phe
1985						1990					1995			
Arg	Tyr	Val	Val	Ile	Ser	Gln	Gly	Leu	Asp	Lys	Pro	Arg	Ala	Ile
2000						2005					2010			
Thr	Val	His	Pro	Glu	Lys	Gly	Tyr	Leu	Phe	Trp	Thr	Glu	Trp	Gly
2015						2020					2025			
Gln	Tyr	Pro	Arg	Ile	Glu	Arg	Ser	Arg	Leu	Asp	Gly	Thr	Glu	Arg
2030						2035					2040			

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Val	Val	Leu	Val	Asn	Val	Ser	Ile	Ser	Trp	Pro	Asn	Gly	Ile	Ser
2045						2050					2055			
Val	Asp	Tyr	Gln	Asp	Gly	Lys	Leu	Tyr	Trp	Cys	Asp	Ala	Arg	Thr
2060						2065					2070			
Asp	Lys	Ile	Glu	Arg	Ile	Asp	Leu	Glu	Thr	Gly	Glu	Asn	Arg	Glu
2075						2080					2085			
Val	Val	Leu	Ser	Ser	Asn	Asn	Met	Asp	Met	Phe	Ser	Val	Ser	Val
2090						2095					2100			
Phe	Glu	Asp	Phe	Ile	Tyr	Trp	Ser	Asp	Arg	Thr	His	Ala	Asn	Gly
2105						2110					2115			
Ser	Ile	Lys	Arg	Gly	Ser	Lys	Asp	Asn	Ala	Thr	Asp	Ser	Val	Pro
2120						2125					2130			
Leu	Arg	Thr	Gly	Ile	Gly	Val	Gln	Leu	Lys	Asp	Ile	Lys	Val	Phe
2135						2140					2145			
Asn	Arg	Asp	Arg	Gln	Lys	Gly	Thr	Asn	Val	Cys	Ala	Val	Ala	Asn
2150						2155					2160			
Gly	Gly	Cys	Gln	Gln	Leu	Cys	Leu	Tyr	Arg	Gly	Arg	Gly	Gln	Arg
2165						2170					2175			
Ala	Cys	Ala	Cys	Ala	His	Gly	Met	Leu	Ala	Glu	Asp	Gly	Ala	Ser
2180						2185					2190			
Cys	Arg	Glu	Tyr	Ala	Gly	Tyr	Leu	Leu	Tyr	Ser	Glu	Arg	Thr	Ile
2195						2200					2205			
Leu	Lys	Ser	Ile	His	Leu	Ser	Asp	Glu	Arg	Asn	Leu	Asn	Ala	Pro
2210						2215					2220			
Val	Gln	Pro	Phe	Glu	Asp	Pro	Glu	His	Met	Lys	Asn	Val	Ile	Ala
2225						2230					2235			
Leu	Ala	Phe	Asp	Tyr	Arg	Ala	Gly	Thr	Ser	Pro	Gly	Thr	Pro	Asn
2240						2245					2250			
Arg	Ile	Phe	Phe	Ser	Asp	Ile	His	Phe	Gly	Asn	Ile	Gln	Gln	Ile
2255						2260					2265			

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Asn	Asp	Asp	Gly	Ser	Arg	Arg	Ile	Thr	Ile	Val	Glu	Asn	Val	Gly
2270						2275					2280			
Ser	Val	Glu	Gly	Leu	Ala	Tyr	His	Arg	Gly	Trp	Asp	Thr	Leu	Tyr
2285						2290					2295			
Trp	Thr	Ser	Tyr	Thr	Thr	Ser	Thr	Ile	Thr	Arg	His	Thr	Val	Asp
2300						2305					2310			
Gln	Thr	Arg	Pro	Gly	Ala	Phe	Glu	Arg	Glu	Thr	Val	Ile	Thr	Met
2315						2320					2325			
Ser	Gly	Asp	Asp	His	Pro	Arg	Ala	Phe	Val	Leu	Asp	Glu	Cys	Gln
2330						2335					2340			
Asn	Leu	Met	Phe	Trp	Thr	Asn	Trp	Asn	Glu	Gln	His	Pro	Ser	Ile
2345						2350					2355			
Met	Arg	Ala	Ala	Leu	Ser	Gly	Ala	Asn	Val	Leu	Thr	Leu	Ile	Glu
2360						2365					2370			
Lys	Asp	Ile	Arg	Thr	Pro	Asn	Gly	Leu	Ala	Ile	Asp	His	Arg	Ala
2375						2380					2385			
Glu	Lys	Leu	Tyr	Phe	Ser	Asp	Ala	Thr	Leu	Asp	Lys	Ile	Glu	Arg
2390						2395					2400			
Cys	Glu	Tyr	Asp	Gly	Ser	His	Arg	Tyr	Val	Ile	Leu	Lys	Ser	Glu
2405						2410					2415			
Pro	Val	His	Pro	Phe	Gly	Leu	Ala	Val	Tyr	Gly	Glu	His	Ile	Phe
2420						2425					2430			
Trp	Thr	Asp	Trp	Val	Arg	Arg	Ala	Val	Gln	Arg	Ala	Asn	Lys	His
2435						2440					2445			
Val	Gly	Ser	Asn	Met	Lys	Leu	Leu	Arg	Val	Asp	Ile	Pro	Gln	Gln
2450						2455					2460			
Pro	Met	Gly	Ile	Ile	Ala	Val	Ala	Asn	Asp	Thr	Asn	Ser	Cys	Glu
2465						2470					2475			
Leu	Ser	Pro	Cys	Arg	Ile	Asn	Asn	Gly	Gly	Cys	Gln	Asp	Leu	Cys
2480						2485					2490			

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Leu	Leu	Thr	His	Gln	Gly	His	Val	Asn	Cys	Ser	Cys	Arg	Gly	Gly
2495						2500					2505			
Arg	Ile	Leu	Gln	Asp	Asp	Leu	Thr	Cys	Arg	Ala	Val	Asn	Ser	Ser
2510						2515					2520			
Cys	Arg	Ala	Gln	Asp	Glu	Phe	Glu	Cys	Ala	Asn	Gly	Glu	Cys	Ile
2525						2530					2535			
Asn	Phe	Ser	Leu	Thr	Cys	Asp	Gly	Val	Pro	His	Cys	Lys	Asp	Lys
2540						2545					2550			
Ser	Asp	Glu	Lys	Pro	Ser	Tyr	Cys	Asn	Ser	Arg	Arg	Cys	Lys	Lys
2555						2560					2565			
Thr	Phe	Arg	Gln	Cys	Ser	Asn	Gly	Arg	Cys	Val	Ser	Asn	Met	Leu
2570						2575					2580			
Trp	Cys	Asn	Gly	Ala	Asp	Asp	Cys	Gly	Asp	Gly	Ser	Asp	Glu	Ile
2585						2590					2595			
Pro	Cys	Asn	Lys	Thr	Ala	Cys	Gly	Val	Gly	Glu	Phe	Arg	Cys	Arg
2600						2605					2610			
Asp	Gly	Thr	Cys	Ile	Gly	Asn	Ser	Ser	Arg	Cys	Asn	Gln	Phe	Val
2615						2620					2625			
Asp	Cys	Glu	Asp	Ala	Ser	Asp	Glu	Met	Asn	Cys	Ser	Ala	Thr	Asp
2630						2635					2640			
Cys	Ser	Ser	Tyr	Phe	Arg	Leu	Gly	Val	Lys	Gly	Val	Leu	Phe	Gln
2645						2650					2655			
Pro	Cys	Glu	Arg	Thr	Ser	Leu	Cys	Tyr	Ala	Pro	Ser	Trp	Val	Cys
2660						2665					2670			
Asp	Gly	Ala	Asn	Asp	Cys	Gly	Asp	Tyr	Ser	Asp	Glu	Arg	Asp	Cys
2675						2680					2685			
Pro	Gly	Val	Lys	Arg	Pro	Arg	Cys	Pro	Leu	Asn	Tyr	Phe	Ala	Cys
2690						2695					2700			
Pro	Ser	Gly	Arg	Cys	Ile	Pro	Met	Ser	Trp	Thr	Cys	Asp	Lys	Glu

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2705		2710		2715
Asp Asp Cys Glu His Gly Glu Asp Glu Thr His Cys Asn Lys Phe	2720	2725	2730	
Cys Ser Glu Ala Gln Phe Glu Cys Gln Asn His Arg Cys Ile Ser	2735	2740	2745	
Lys Gln Trp Leu Cys Asp Gly Ser Asp Asp Cys Gly Asp Gly Ser	2750	2755	2760	
Asp Glu Ala Ala His Cys Glu Gly Lys Thr Cys Gly Pro Ser Ser	2765	2770	2775	
Phe Ser Cys Pro Gly Thr His Val Cys Val Pro Glu Arg Trp Leu	2780	2785	2790	
Cys Asp Gly Asp Lys Asp Cys Ala Asp Gly Ala Asp Glu Ser Ile	2795	2800	2805	
Ala Ala Gly Cys Leu Tyr Asn Ser Thr Cys Asp Asp Arg Glu Phe	2810	2815	2820	
Met Cys Gln Asn Arg Gln Cys Ile Pro Lys His Phe Val Cys Asp	2825	2830	2835	
His Asp Arg Asp Cys Ala Asp Gly Ser Asp Glu Ser Pro Glu Cys	2840	2845	2850	
Glu Tyr Pro Thr Cys Gly Pro Ser Glu Phe Arg Cys Ala Asn Gly	2855	2860	2865	
Arg Cys Leu Ser Ser Arg Gln Trp Glu Cys Asp Gly Glu Asn Asp	2870	2875	2880	
Cys His Asp Gln Ser Asp Glu Ala Pro Lys Asn Pro His Cys Thr	2885	2890	2895	
Ser Pro Glu His Lys Cys Asn Ala Ser Ser Gln Phe Leu Cys Ser	2900	2905	2910	
Ser Gly Arg Cys Val Ala Glu Ala Leu Leu Cys Asn Gly Gln Asp	2915	2920	2925	

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Asp	Cys	Gly	Asp	Ser	Ser	Asp	Glu	Arg	Gly	Cys	His	Ile	Asn	Glu
2930						2935					2940			
Cys	Leu	Ser	Arg	Lys	Leu	Ser	Gly	Cys	Ser	Gln	Asp	Cys	Glu	Asp
2945						2950					2955			
Leu	Lys	Ile	Gly	Phe	Lys	Cys	Arg	Cys	Arg	Pro	Gly	Phe	Arg	Leu
2960						2965					2970			
Lys	Asp	Asp	Gly	Arg	Thr	Cys	Ala	Asp	Val	Asp	Glu	Cys	Ser	Thr
2975						2980					2985			
Thr	Phe	Pro	Cys	Ser	Gln	Arg	Cys	Ile	Asn	Thr	His	Gly	Ser	Tyr
2990						2995					3000			
Lys	Cys	Leu	Cys	Val	Glu	Gly	Tyr	Ala	Pro	Arg	Gly	Gly	Asp	Pro
3005						3010					3015			
His	Ser	Cys	Lys	Ala	Val	Thr	Asp	Glu	Glu	Pro	Phe	Leu	Ile	Phe
3020						3025					3030			
Ala	Asn	Arg	Tyr	Tyr	Leu	Arg	Lys	Leu	Asn	Leu	Asp	Gly	Ser	Asn
3035						3040					3045			
Tyr	Thr	Leu	Leu	Lys	Gln	Gly	Leu	Asn	Asn	Ala	Val	Ala	Leu	Asp
3050						3055					3060			
Phe	Asp	Tyr	Arg	Glu	Gln	Met	Ile	Tyr	Trp	Thr	Asp	Val	Thr	Thr
3065						3070					3075			
Gln	Gly	Ser	Met	Ile	Arg	Arg	Met	His	Leu	Asn	Gly	Ser	Asn	Val
3080						3085					3090			
Gln	Val	Leu	His	Arg	Thr	Gly	Leu	Ser	Asn	Pro	Asp	Gly	Leu	Ala
3095						3100					3105			
Val	Asp	Trp	Val	Gly	Gly	Asn	Leu	Tyr	Trp	Cys	Asp	Lys	Gly	Arg
3110						3115					3120			
Asp	Thr	Ile	Glu	Val	Ser	Lys	Leu	Asn	Gly	Ala	Tyr	Arg	Thr	Val
3125						3130					3135			
Leu	Val	Ser	Ser	Gly	Leu	Arg	Glu	Pro	Arg	Ala	Leu	Val	Val	Asp
3140						3145					3150			

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Val Gln Asn Gly Tyr Leu Tyr Trp Thr Asp Trp Gly Asp His Ser
 3155 3160 3165
 Leu Ile Gly Arg Ile Gly Met Asp Gly Ser Ser Arg Ser Val Ile
 3170 3175 3180
 Val Asp Thr Lys Ile Thr Trp Pro Asn Gly Leu Thr Leu Asp Tyr
 3185 3190 3195
 Val Thr Glu Arg Ile Tyr Trp Ala Asp Ala Arg Glu Asp Tyr Ile
 3200 3205 3210
 Glu Phe Ala Ser Leu Asp Gly Ser Asn Arg His Val Val Leu Ser
 3215 3220 3225
 Gln Asp Ile Pro His Ile Phe Ala Leu Thr Leu Phe Glu Asp Tyr
 3230 3235 3240
 Val Tyr Trp Thr Asp Trp Glu Thr Lys Ser Ile Asn Arg Ala His
 3245 3250 3255
 Lys Thr Thr Gly Thr Asn Lys Thr Leu Leu Ile Ser Thr Leu His
 3260 3265 3270
 Arg Pro Met Asp Leu His Val Phe His Ala Leu Arg Gln Pro Asp
 3275 3280 3285
 Val Pro Asn His Pro Cys Lys Val Asn Asn Gly Gly Cys Ser Asn
 3290 3295 3300
 Leu Cys Leu Leu Ser Pro Gly Gly Gly His Lys Cys Ala Cys Pro
 3305 3310 3315
 Thr Asn Phe Tyr Leu Gly Ser Asp Gly Arg Thr Cys Val Ser Asn
 3320 3325 3330
 Cys Thr Ala Ser Gln Phe Val Cys Lys Asn Asp Lys Cys Ile Pro
 3335 3340 3345
 Phe Trp Trp Lys Cys Asp Thr Glu Asp Asp Cys Gly Asp His Ser
 3350 3355 3360
 Asp Glu Pro Pro Asp Cys Pro Glu Phe Lys Cys Arg Pro Gly Gln
 3365 3370 3375

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Phe Gln Cys Ser Thr Gly Ile Cys Thr Asn Pro Ala Phe Ile Cys
 3380 3385 3390
 Asp Gly Asp Asn Asp Cys Gln Asp Asn Ser Asp Glu Ala Asn Cys
 3395 3400 3405
 Asp Ile His Val Cys Leu Pro Ser Gln Phe Lys Cys Thr Asn Thr
 3410 3415 3420
 Asn Arg Cys Ile Pro Gly Ile Phe Arg Cys Asn Gly Gln Asp Asn
 3425 3430 3435
 Cys Gly Asp Gly Glu Asp Glu Arg Asp Cys Pro Glu Val Thr Cys
 3440 3445 3450
 Ala Pro Asn Gln Phe Gln Cys Ser Ile Thr Lys Arg Cys Ile Pro
 3455 3460 3465
 Arg Val Trp Val Cys Asp Arg Asp Asn Asp Cys Val Asp Gly Ser
 3470 3475 3480
 Asp Glu Pro Ala Asn Cys Thr Gln Met Thr Cys Gly Val Asp Glu
 3485 3490 3495
 Phe Arg Cys Lys Asp Ser Gly Arg Cys Ile Pro Ala Arg Trp Lys
 3500 3505 3510
 Cys Asp Gly Glu Asp Asp Cys Gly Asp Gly Ser Asp Glu Pro Lys
 3515 3520 3525
 Glu Glu Cys Asp Glu Arg Thr Cys Glu Pro Tyr Gln Phe Arg Cys
 3530 3535 3540
 Lys Asn Asn Arg Cys Val Pro Gly Arg Trp Gln Cys Asp Tyr Asp
 3545 3550 3555
 Asn Asp Cys Gly Asp Asn Ser Asp Glu Glu Ser Cys Thr Pro Arg
 3560 3565 3570
 Pro Cys Ser Glu Ser Glu Phe Ser Cys Ala Asn Gly Arg Cys Ile
 3575 3580 3585
 Ala Gly Arg Trp Lys Cys Asp Gly Asp His Asp Cys Ala Asp Gly

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3590		3595		3600
Ser Asp Glu Lys Asp Cys Thr Pro Arg Cys Asp Met Asp Gln Phe				
3605		3610		3615
Gln Cys Lys Ser Gly His Cys Ile Pro Leu Arg Trp Arg Cys Asp				
3620		3625		3630
Ala Asp Ala Asp Cys Met Asp Gly Ser Asp Glu Glu Ala Cys Gly				
3635		3640		3645
Thr Gly Val Arg Thr Cys Pro Leu Asp Glu Phe Gln Cys Asn Asn				
3650		3655		3660
Thr Leu Cys Lys Pro Leu Ala Trp Lys Cys Asp Gly Glu Asp Asp				
3665		3670		3675
Cys Gly Asp Asn Ser Asp Glu Asn Pro Glu Glu Cys Ala Arg Phe				
3680		3685		3690
Val Cys Pro Pro Asn Arg Pro Phe Arg Cys Lys Asn Asp Arg Val				
3695		3700		3705
Cys Leu Trp Ile Gly Arg Gln Cys Asp Gly Thr Asp Asn Cys Gly				
3710		3715		3720
Asp Gly Thr Asp Glu Glu Asp Cys Glu Pro Pro Thr Ala His Thr				
3725		3730		3735
Thr His Cys Lys Asp Lys Lys Glu Phe Leu Cys Arg Asn Gln Arg				
3740		3745		3750
Cys Leu Ser Ser Ser Leu Arg Cys Asn Met Phe Asp Asp Cys Gly				
3755		3760		3765
Asp Gly Ser Asp Glu Glu Asp Cys Ser Ile Asp Pro Lys Leu Thr				
3770		3775		3780
Ser Cys Ala Thr Asn Ala Ser Ile Cys Gly Asp Glu Ala Arg Cys				
3785		3790		3795
Val Arg Thr Glu Lys Ala Ala Tyr Cys Ala Cys Arg Ser Gly Phe				
3800		3805		3810

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His Thr	Val Pro Gly Gln	Pro Gly Cys Gln Asp	Ile Asn Glu Cys
3815		3820	3825
Leu Arg	Phe Gly Thr Cys	Ser Gln Leu Cys Asn	Asn Thr Lys Gly
3830		3835	3840
Gly His	Leu Cys Ser Cys	Ala Arg Asn Phe Met	Lys Thr His Asn
3845		3850	3855
Thr Cys	Lys Ala Glu Gly	Ser Glu Tyr Gln Val	Leu Tyr Ile Ala
3860		3865	3870
Asp Asp	Asn Glu Ile Arg	Ser Leu Phe Pro Gly	His Pro His Ser
3875		3880	3885
Ala Tyr	Glu Gln Ala Phe	Gln Gly Asp Glu Ser	Val Arg Ile Asp
3890		3895	3900
Ala Met	Asp Val His Val	Lys Ala Gly Arg Val	Tyr Trp Thr Asn
3905		3910	3915
Trp His	Thr Gly Thr Ile	Ser Tyr Arg Ser Leu	Pro Pro Ala Ala
3920		3925	3930
Pro Pro	Thr Thr Ser Asn	Arg His Arg Arg Gln	Ile Asp Arg Gly
3935		3940	3945
Val Thr	His Leu Asn Ile	Ser Gly Leu Lys Met	Pro Arg Gly Ile
3950		3955	3960
Ala Ile	Asp Trp Val Ala	Gly Asn Val Tyr Trp	Thr Asp Ser Gly
3965		3970	3975
Arg Asp	Val Ile Glu Val	Ala Gln Met Lys Gly	Glu Asn Arg Lys
3980		3985	3990
Thr Leu	Ile Ser Gly Met	Ile Asp Glu Pro His	Ala Ile Val Val
3995		4000	4005
Asp Pro	Leu Arg Gly Thr	Met Tyr Trp Ser Asp	Trp Gly Asn His
4010		4015	4020
Pro Lys	Ile Glu Thr Ala	Ala Met Asp Gly Thr	Leu Arg Glu Thr
4025		4030	4035

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Leu Val Gln Asp Asn Ile Gln Trp Pro Thr Gly Leu Ala Val Asp
 4040 4045 4050
 Tyr His Asn Glu Arg Leu Tyr Trp Ala Asp Ala Lys Leu Ser Val
 4055 4060 4065
 Ile Gly Ser Ile Arg Leu Asn Gly Thr Asp Pro Ile Val Ala Ala
 4070 4075 4080
 Asp Ser Lys Arg Gly Leu Ser His Pro Phe Ser Ile Asp Val Phe
 4085 4090 4095
 Glu Asp Tyr Ile Tyr Gly Val Thr Tyr Ile Asn Asn Arg Val Phe
 4100 4105 4110
 Lys Ile His Lys Phe Gly His Ser Pro Leu Val Asn Leu Thr Gly
 4115 4120 4125
 Gly Leu Ser His Ala Ser Asp Val Val Leu Tyr His Gln His Lys
 4130 4135 4140
 Gln Pro Glu Val Thr Asn Pro Cys Asp Arg Lys Lys Cys Glu Trp
 4145 4150 4155
 Leu Cys Leu Leu Ser Pro Ser Gly Pro Val Cys Thr Cys Pro Asn
 4160 4165 4170
 Gly Lys Arg Leu Asp Asn Gly Thr Cys Val Pro Val Pro Ser Pro
 4175 4180 4185
 Thr Pro Pro Pro Asp Ala Pro Arg Pro Gly Thr Cys Asn Leu Gln
 4190 4195 4200
 Cys Phe Asn Gly Gly Ser Cys Phe Leu Asn Ala Arg Arg Gln Pro
 4205 4210 4215
 Lys Cys Arg Cys Gln Pro Arg Tyr Thr Gly Asp Lys Cys Glu Leu
 4220 4225 4230
 Asp Gln Cys Trp Glu His Cys Arg Asn Gly Gly Thr Cys Ala Ala
 4235 4240 4245
 Ser Pro Ser Gly Met Pro Thr Cys Arg Cys Pro Thr Gly Phe Thr
 4250 4255 4260

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Gly Pro Lys Cys Thr Gln Gln Val Cys Ala Gly Tyr Cys Ala Asn
 4265 4270 4275

Asn Ser Thr Cys Thr Val Asn Gln Gly Asn Gln Pro Gln Cys Arg
 4280 4285 4290

Cys Leu Pro Gly Phe Leu Gly Asp Arg Cys Gln Tyr Arg Gln Cys
 4295 4300 4305

Ser Gly Tyr Cys Glu Asn Phe Gly Thr Cys Gln Met Ala Ala Asp
 4310 4315 4320

Gly Ser Arg Gln Cys Arg Cys Thr Ala Tyr Phe Glu Gly Ser Arg
 4325 4330 4335

Cys Glu Val Asn Lys Cys Ser Arg Cys Leu Glu Gly Ala Cys Val
 4340 4345 4350

Val Asn Lys Gln Ser Gly Asp Val Thr Cys Asn Cys Thr Asp Gly
 4355 4360 4365

Arg Val Ala Pro Ser Cys Leu Thr Cys Val Gly His Cys Ser Asn
 4370 4375 4380

Gly Gly Ser Cys Thr Met Asn Ser Lys Met Met Pro Glu Cys Gln
 4385 4390 4395

Cys Pro Pro His Met Thr Gly Pro Arg Cys Glu Glu His Val Phe
 4400 4405 4410

Ser Gln Gln Gln Pro Gly His Ile Ala Ser Ile Leu Ile Pro Leu
 4415 4420 4425

Leu Leu Leu Leu Leu Leu Val Leu Val Ala Gly Val Val Phe Trp
 4430 4435 4440

Tyr Lys Arg Arg Val Gln Gly Ala Lys Gly Phe Gln His Gln Arg
 4445 4450 4455

Met Thr Asn Gly Ala Met Asn Val Glu Ile Gly Asn Pro Thr Tyr
 4460 4465 4470

Lys Met Tyr Glu Gly Gly Glu Pro Asp Asp Val Gly Gly Leu Leu

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4475 4480 4485
 Asp Ala Asp Phe Ala Leu Asp Pro Asp Lys Pro Thr Asn Phe Thr
 4490 4495 4500

 Asn Pro Val Tyr Ala Thr Leu Tyr Met Gly Gly His Gly Ser Arg
 4505 4510 4515

 His Ser Leu Ala Ser Thr Asp Glu Lys Arg Glu Leu Leu Gly Arg
 4520 4525 4530

 Gly Pro Glu Asp Glu Ile Gly Asp Pro Leu Ala
 4535 4540

 <210> 113
 .
 <211> 113
 <212> PRT
 <213> Homo sapiens

 <400> 113
 Met Gly Gly Leu Glu Pro Cys Ser Arg Leu Leu Leu Leu Pro Leu Leu
 1 5 10 15

 Leu Ala Val Ser Gly Leu Arg Pro Val Gln Ala Gln Ala Gln Ser Asp
 20 25 30

 Cys Ser Cys Ser Thr Val Ser Pro Gly Val Leu Ala Gly Ile Val Met
 35 40 45

 Gly Asp Leu Val Leu Thr Val Leu Ile Ala Leu Ala Val Tyr Phe Leu
 50 55 60

 Gly Arg Leu Val Pro Arg Gly Arg Gly Ala Ala Glu Ala Ala Thr Arg
 65 70 75 80

 Lys Gln Arg Ile Thr Glu Thr Glu Ser Pro Tyr Gln Glu Leu Gln Gly
 85 90 95

 Gln Arg Ser Asp Val Tyr Ser Asp Leu Asn Thr Gln Arg Pro Tyr Tyr
 100 105 110

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Lys

<210> 114

<211> 281

<212> PRT

<213> Homo sapiens

<400> 114

Met Gly His Pro Pro Leu Leu Pro Leu Leu Leu Leu Leu His Thr Cys
 1 5 10 15

Val Pro Ala Ser Trp Gly Leu Arg Cys Met Gln Cys Lys Thr Asn Gly
 20 25 30

Asp Cys Arg Val Glu Glu Cys Ala Leu Gly Gln Asp Leu Cys Arg Thr
 35 40 45

Thr Ile Val Arg Leu Trp Glu Glu Gly Glu Glu Leu Glu Leu Val Glu
 50 55 60

Lys Ser Cys Thr His Ser Glu Lys Thr Asn Arg Thr Leu Ser Tyr Arg
 65 70 75 80

Thr Gly Leu Lys Ile Thr Ser Leu Thr Glu Val Val Cys Gly Leu Asp
 85 90 95

Leu Cys Asn Gln Gly Asn Ser Gly Arg Ala Val Thr Tyr Ser Arg Ser
 100 105 110

Arg Tyr Leu Glu Cys Ile Ser Cys Gly Ser Ser Asp Met Ser Cys Glu
 115 120 125

Arg Gly Arg His Gln Ser Leu Gln Cys Arg Ser Pro Glu Glu Gln Cys
 130 135 140

Leu Asp Val Val Thr His Trp Ile Gln Glu Gly Glu Glu Gly Arg Pro
 145 150 155 160

Lys Asp Asp Arg His Leu Arg Gly Cys Gly Tyr Leu Pro Gly Cys Pro
 165 170 175

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Gly Ser Asn Gly Phe His Asn Asn Asp Thr Phe His Phe Leu Lys Cys
 180 185 190

Cys Asn Thr Thr Lys Cys Asn Glu Gly Pro Ile Leu Glu Leu Glu Asn
 195 200 205

Leu Pro Gln Asn Gly Arg Gln Cys Tyr Ser Cys Lys Gly Asn Ser Thr
 210 215 220

His Gly Cys Ser Ser Glu Glu Thr Phe Leu Ile Asp Cys Arg Gly Pro
 225 230 235 240

Met Asn Gln Cys Leu Val Ala Thr Gly Thr His Glu Arg Ser Leu Trp
 245 250 255

Gly Ser Trp Leu Pro Cys Lys Ser Thr Thr Ala Leu Arg Pro Pro Cys
 260 265 270

Cys Glu Glu Ala Gln Ala Thr His Val
 275 280

<210> 115

<211> 351

<212> PRT

<213> Homo sapiens

<400> 115

Met Glu Thr Asn Phe Ser Thr Pro Leu Asn Glu Tyr Glu Glu Val Ser
 1 5 10 15

Tyr Glu Ser Ala Gly Tyr Thr Val Leu Arg Ile Leu Pro Leu Val Val
 20 25 30

Leu Gly Val Thr Phe Val Leu Gly Val Leu Gly Asn Gly Leu Val Ile
 35 40 45

Trp Val Ala Gly Phe Arg Met Thr Arg Thr Val Thr Thr Ile Cys Tyr
 50 55 60

Leu Asn Leu Ala Leu Ala Asp Phe Ser Phe Thr Ala Thr Leu Pro Phe
 65 70 75 80

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Leu Ile Val Ser Met Ala Met Gly Glu Lys Trp Pro Phe Gly Trp Phe
85 90 95

Leu Cys Lys Leu Ile His Ile Val Val Asp Ile Asn Leu Phe Gly Ser
100 105 110

Val Phe Leu Ile Gly Phe Ile Ala Leu Asp Arg Cys Ile Cys Val Leu
115 120 125

His Pro Val Trp Ala Gln Asn His Arg Thr Val Ser Leu Ala Met Lys
130 135 140

Val Ile Val Gly Pro Trp Ile Leu Ala Leu Val Leu Thr Leu Pro Val
145 150 155 160

Phe Leu Phe Leu Thr Thr Val Thr Ile Pro Asn Gly Asp Thr Tyr Cys
165 170 175

Thr Phe Asn Phe Ala Ser Trp Gly Gly Thr Pro Glu Glu Arg Leu Lys
180 185 190

Val Ala Ile Thr Met Leu Thr Ala Arg Gly Ile Ile Arg Phe Val Ile
195 200 205

Gly Phe Ser Leu Pro Met Ser Ile Val Ala Ile Cys Tyr Gly Leu Ile
210 215 220

Ala Ala Lys Ile His Lys Lys Gly Met Ile Lys Ser Ser Arg Pro Leu
225 230 235 240

Arg Val Leu Thr Ala Val Val Ala Ser Phe Phe Ile Cys Trp Phe Pro
245 250 255

Phe Gln Leu Val Ala Leu Leu Gly Thr Val Trp Leu Lys Glu Met Leu
260 265 270

Phe Tyr Gly Lys Tyr Lys Ile Ile Asp Ile Leu Val Asn Pro Thr Ser
275 280 285

Ser Leu Ala Phe Phe Asn Ser Cys Leu Asn Pro Met Leu Tyr Val Phe
290 295 300

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Val Gly Gln Asp Phe Arg Glu Arg Leu Ile His Ser Leu Pro Thr Ser
 305 310 315 320

Leu Glu Arg Ala Leu Ser Glu Asp Ser Ala Pro Thr Asn Asp Thr Ala
 325 330 335

Ala Asn Ser Ala Ser Pro Pro Ala Glu Thr Glu Leu Gln Ala Met
 340 345 350

<210> 116

<211> 299

<212> PRT

<213> Homo sapiens

<400> 116

Met Arg Asp Arg Leu Pro Asp Leu Thr Ala Cys Arg Lys Asn Asp Asp
 1 5 10 15

Gly Asp Thr Val Val Val Val Glu Lys Asp His Phe Met Asp Asp Phe
 20 25 30

Phe His Gln Val Glu Glu Ile Arg Asn Ser Ile Asp Lys Ile Thr Gln
 35 40 45

Tyr Val Glu Glu Val Lys Lys Asn His Ser Ile Ile Leu Ser Ala Pro
 50 55 60

Asn Pro Glu Gly Lys Ile Lys Glu Glu Leu Glu Asp Leu Asn Lys Glu
 65 70 75 80

Ile Lys Lys Thr Ala Asn Lys Ile Ala Ala Lys Leu Lys Ala Ile Glu
 85 90 95

Gln Ser Phe Asp Gln Asp Glu Ser Gly Asn Arg Thr Ser Val Asp Leu
 100 105 110

Arg Ile Arg Arg Thr Gln His Ser Val Leu Ser Arg Lys Phe Val Glu
 115 120 125

Ala Met Ala Glu Tyr Asn Glu Ala Gln Thr Leu Phe Arg Glu Arg Ser
 130 135 140

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Lys Gly Arg Ile Gln Arg Gln Leu Glu Ile Thr Gly Arg Thr Thr Thr
 145 150 155 160

Asp Asp Glu Leu Glu Glu Met Leu Glu Ser Gly Lys Pro Ser Ile Phe
 165 170 175

Thr Ser Asp Ile Ile Ser Asp Ser Gln Ile Thr Arg Gln Ala Leu Asn
 180 185 190

Glu Ile Glu Ser Arg His Lys Asp Ile Met Lys Leu Glu Thr Ser Ile
 195 200 205

Arg Glu Leu His Glu Met Phe Met Asp Met Ala Met Phe Val Glu Thr
 210 215 220

Gln Gly Glu Met Ile Asn Asn Ile Glu Arg Asn Val Met Asn Ala Thr
 225 230 235 240

Asp Tyr Val Glu His Ala Lys Glu Glu Thr Lys Lys Ala Ile Lys Tyr
 245 250 255

Gln Ser Lys Ala Arg Arg Lys Lys Trp Ile Ile Ile Ala Val Ser Val
 260 265 270

Val Leu Val Val Tyr Arg Leu Phe Gly Leu Ser Leu Glu Tyr Val Val
 275 280 285

Arg Ser Ala Ala Ser Leu Pro Gly Trp Gly Asn
 290 295

<210> 117

<211> 836

<212> PRT

<213> Homo sapiens

<400> 117

Met Ala Arg Leu Gly Asn Cys Ser Leu Thr Trp Ala Ala Leu Ile Ile
 1 5 10 15

Leu Leu Leu Pro Gly Ser Leu Glu Glu Cys Gly His Ile Ser Val Ser
 20 25 30

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Ala Pro Ile Val His Leu Gly Asp Pro Ile Thr Ala Ser Cys Ile Ile
35 40 45

Lys Gln Asn Cys Ser His Leu Asp Pro Glu Pro Gln Ile Leu Trp Arg
50 55 60

Leu Gly Ala Glu Leu Gln Pro Gly Gly Arg Gln Gln Arg Leu Ser Asp
65 70 75 80

Gly Thr Gln Glu Ser Ile Ile Thr Leu Pro His Leu Asn His Thr Gln
85 90 95

Ala Phe Leu Ser Cys Cys Leu Asn Trp Gly Asn Ser Leu Gln Ile Leu
100 105 110

Asp Gln Val Glu Leu Arg Ala Gly Tyr Pro Pro Ala Ile Pro His Asn
115 120 125

Leu Ser Cys Leu Met Asn Leu Thr Thr Ser Ser Leu Ile Cys Gln Trp
130 135 140

Glu Pro Gly Pro Glu Thr His Leu Pro Thr Ser Phe Thr Leu Lys Ser
145 150 155 160

Phe Lys Ser Arg Gly Asn Cys Gln Thr Gln Gly Asp Ser Ile Leu Asp
165 170 175

Cys Val Pro Lys Asp Gly Gln Ser His Cys Cys Ile Pro Arg Lys His
180 185 190

Leu Leu Leu Tyr Gln Asn Met Gly Ile Trp Val Gln Ala Glu Asn Ala
195 200 205

Leu Gly Thr Ser Met Ser Pro Gln Leu Cys Leu Asp Pro Met Asp Val
210 215 220

Val Lys Leu Glu Pro Pro Met Leu Arg Thr Met Asp Pro Ser Pro Glu
225 230 235 240

Ala Ala Pro Pro Gln Ala Gly Cys Leu Gln Leu Cys Trp Glu Pro Trp
245 250 255

Gln Pro Gly Leu His Ile Asn Gln Lys Cys Glu Leu Arg His Lys Pro

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260	265	270
Gln Arg Gly Glu Ala Ser Trp Ala Leu Val Gly Pro Leu Pro Leu Glu 275 280 285		
Ala Leu Gln Tyr Glu Leu Cys Gly Leu Leu Pro Ala Thr Ala Tyr Thr 290 295 300		
Leu Gln Ile Arg Cys Ile Arg Trp Pro Leu Pro Gly His Trp Ser Asp 305 310 315 320		
Trp Ser Pro Ser Leu Glu Leu Arg Thr Thr Glu Arg Ala Pro Thr Val 325 330 335		
Arg Leu Asp Thr Trp Trp Arg Gln Arg Gln Leu Asp Pro Arg Thr Val 340 345 350		
Gln Leu Phe Trp Lys Pro Val Pro Leu Glu Glu Asp Ser Gly Arg Ile 355 360 365		
Gln Gly Tyr Val Val Ser Trp Arg Pro Ser Gly Gln Ala Gly Ala Ile 370 375 380		
Leu Pro Leu Cys Asn Thr Thr Glu Leu Ser Cys Thr Phe His Leu Pro 385 390 395 400		
Ser Glu Ala Gln Glu Val Ala Leu Val Ala Tyr Asn Ser Ala Gly Thr 405 410 415		
Ser Arg Pro Thr Pro Val Val Phe Ser Glu Ser Arg Gly Pro Ala Leu 420 425 430		
Thr Arg Leu His Ala Met Ala Arg Asp Pro His Ser Leu Trp Val Gly 435 440 445		
Trp Glu Pro Pro Asn Pro Trp Pro Gln Gly Tyr Val Ile Glu Trp Gly 450 455 460		
Leu Gly Pro Pro Ser Ala Ser Asn Ser Asn Lys Thr Trp Arg Met Glu 465 470 475 480		
Gln Asn Gly Arg Ala Thr Gly Phe Leu Leu Lys Glu Asn Ile Arg Pro 485 490 495		

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Phe Gln Leu Tyr Glu Ile Ile Val Thr Pro Leu Tyr Gln Asp Thr Met
 500 505 510

Gly Pro Ser Gln His Val Tyr Ala Tyr Ser Gln Glu Met Ala Pro Ser
 515 520 525

His Ala Pro Glu Leu His Leu Lys His Ile Gly Lys Thr Trp Ala Gln
 530 535 540

Leu Glu Trp Val Pro Glu Pro Pro Glu Leu Gly Lys Ser Pro Leu Thr
 545 550 555 560

His Tyr Thr Ile Phe Trp Thr Asn Ala Gln Asn Gln Ser Phe Ser Ala
 565 570 575

Ile Leu Asn Ala Ser Ser Arg Gly Phe Val Leu His Gly Leu Glu Pro
 580 585 590

Ala Ser Leu Tyr His Ile His Leu Met Ala Ala Ser Gln Ala Gly Ala
 595 600 605

Thr Asn Ser Thr Val Leu Thr Leu Met Thr Leu Thr Pro Glu Gly Ser
 610 615 620

Glu Leu His Ile Ile Leu Gly Leu Phe Gly Leu Leu Leu Leu Leu Thr
 625 630 635 640

Cys Leu Cys Gly Thr Ala Trp Leu Cys Cys Ser Pro Asn Arg Lys Asn
 645 650 655

Pro Leu Trp Pro Ser Val Pro Asp Pro Ala His Ser Ser Leu Gly Ser
 660 665 670

Trp Val Pro Thr Ile Met Glu Glu Asp Ala Phe Gln Leu Pro Gly Leu
 675 680 685

Gly Thr Pro Pro Ile Thr Lys Leu Thr Val Leu Glu Glu Asp Glu Lys
 690 695 700

Lys Pro Val Pro Trp Glu Ser His Asn Ser Ser Glu Thr Cys Gly Leu
 705 710 715 720

Pro Thr Leu Val Gln Thr Tyr Val Leu Gln Gly Asp Pro Arg Ala Val
 725 730 735

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Ser Thr Gln Pro Gln Ser Gln Ser Gly Thr Ser Asp Gln Val Leu Tyr
740 745 750

Gly Gln Leu Leu Gly Ser Pro Thr Ser Pro Gly Pro Gly His Tyr Leu
755 760 765

Arg Cys Asp Ser Thr Gln Pro Leu Leu Ala Gly Leu Thr Pro Ser Pro
770 775 780

Lys Ser Tyr Glu Asn Leu Trp Phe Gln Ala Ser Pro Leu Gly Thr Leu
785 790 795 800

Val Thr Pro Ala Pro Ser Gln Glu Asp Asp Cys Val Phe Gly Pro Leu
805 810 815

Leu Asn Phe Pro Leu Leu Gln Gly Ile Arg Val His Gly Met Glu Ala
820 825 830

Leu Gly Ser Phe
835

<210> 118

<211> 540

<212> PRT

<213> Homo sapiens

<400> 118

Met Arg Val Ala Ala Ala Thr Ala Ala Ala Gly Ala Gly Pro Ala Met
1 5 10 15

Ala Val Trp Thr Arg Ala Thr Lys Ala Gly Leu Val Glu Leu Leu Leu
20 25 30

Arg Glu Arg Trp Val Arg Val Val Ala Glu Leu Ser Gly Glu Ser Leu
35 40 45

Ser Leu Thr Gly Asp Ala Ala Ala Ala Glu Leu Glu Pro Ala Leu Gly
50 55 60

Pro Ala Ala Ala Ala Phe Asn Gly Leu Pro Asn Gly Gly Gly Ala Gly
65 70 75 80

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Asp Ser Leu Pro Gly Ser Pro Ser Arg Gly Leu Gly Pro Pro Ser Pro
 85 90 95

Pro Ala Pro Pro Arg Gly Pro Ala Gly Glu Ala Gly Ala Ser Pro Pro
 100 105 110

Val Arg Arg Val Arg Val Val Lys Gln Glu Ala Gly Gly Leu Gly Ile
 115 120 125

Ser Ile Lys Gly Gly Arg Glu Asn Arg Met Pro Ile Leu Ile Ser Lys
 130 135 140

Ile Phe Pro Gly Leu Ala Ala Asp Gln Ser Arg Ala Leu Arg Leu Gly
 145 150 155 160

Asp Ala Ile Leu Ser Val Asn Gly Thr Asp Leu Arg Gln Ala Thr His
 165 170 175

Asp Gln Ala Val Gln Ala Leu Lys Arg Ala Gly Lys Glu Val Leu Leu
 180 185 190

Glu Val Lys Phe Ile Arg Glu Val Thr Pro Tyr Ile Lys Lys Pro Ser
 195 200 205

Leu Val Ser Asp Leu Pro Trp Glu Gly Ala Ala Pro Gln Ser Pro Ser
 210 215 220

Phe Ser Gly Ser Glu Asp Ser Gly Ser Pro Lys His Gln Asn Ser Thr
 225 230 235 240

Lys Asp Arg Lys Ile Ile Pro Leu Lys Met Cys Phe Ala Ala Arg Asn
 245 250 255

Leu Ser Met Pro Asp Leu Glu Asn Arg Leu Ile Glu Leu His Ser Pro
 260 265 270

Asp Ser Arg Asn Thr Leu Ile Leu Arg Cys Lys Asp Thr Ala Thr Ala
 275 280 285

His Ser Trp Phe Val Ala Ile His Thr Asn Ile Met Ala Leu Leu Pro
 290 295 300

Gln Val Leu Ala Glu Leu Asn Ala Met Leu Gly Ala Thr Ser Thr Ala

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305		310		315		320
Gly Gly Ser Lys	Glu Val Lys His Ile	Ala Trp Leu Ala	Glu Gln Ala			
	325	330	335			
Lys Leu Asp	Gly Gly Arg Gln Gln	Trp Arg Pro Val	Leu Met Ala Val			
	340	345	350			
Thr Glu Lys Asp	Leu Leu Leu Tyr Asp	Cys Met Pro Trp	Thr Arg Asp			
	355	360	365			
Ala Trp Ala Ser	Pro Cys His Ser Tyr	Pro Leu Val Ala	Thr Arg Leu			
	370	375	380			
Val His Ser Gly	Ser Gly Cys Arg Ser	Pro Ser Leu Gly	Ser Asp Leu			
	385	390	395	400		
Thr Phe Ala Thr	Arg Thr Gly Ser Arg	Gln Gly Ile Glu	Met His Leu			
	405	410	415			
Phe Arg Val Glu	Thr His Arg Asp	Leu Ser Ser Trp	Thr Arg Ile Leu			
	420	425	430			
Val Gln Gly Cys	His Ala Ala Ala	Glu Leu Ile Lys	Glu Val Ser Leu			
	435	440	445			
Gly Cys Met Leu	Asn Gly Gln Glu Val	Arg Leu Thr Ile	His Tyr Glu			
	450	455	460			
Asn Gly Phe Thr	Ile Ser Arg Glu Asn	Gly Gly Ser Ser	Ser Ile Leu			
	465	470	475	480		
Tyr Arg Tyr Pro	Phe Glu Arg Leu Lys	Met Ser Ala Asp	Asp Gly Ile			
	485	490	495			
Arg Asn Leu Tyr	Leu Asp Phe Gly Gly	Pro Glu Gly Glu	Leu Thr Met			
	500	505	510			
Asp Leu His Ser	Cys Pro Lys Pro	Ile Val Phe Val	Leu His Thr Phe			
	515	520	525			
Leu Ser Ala Lys	Val Thr Arg Met	Gly Leu Leu Val				
	530	535	540			

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<210> 119

<211> 250

<212> PRT

<213> Homo sapiens

<400> 119

Met Ala Asp Asn Phe Ser Leu His Asp Ala Leu Ser Gly Ser Gly Asn
 1 5 10 15

Pro Asn Pro Gln Gly Trp Pro Gly Ala Trp Gly Asn Gln Pro Ala Gly
 20 25 30

Ala Gly Gly Tyr Pro Gly Ala Ser Tyr Pro Gly Ala Tyr Pro Gly Gln
 35 40 45

Ala Pro Pro Gly Ala Tyr Pro Gly Gln Ala Pro Pro Gly Ala Tyr Pro
 50 55 60

Gly Ala Pro Gly Ala Tyr Pro Gly Ala Pro Ala Pro Gly Val Tyr Pro
 65 70 75 80

Gly Pro Pro Ser Gly Pro Gly Ala Tyr Pro Ser Ser Gly Gln Pro Ser
 85 90 95

Ala Thr Gly Ala Tyr Pro Ala Thr Gly Pro Tyr Gly Ala Pro Ala Gly
 100 105 110

Pro Leu Ile Val Pro Tyr Asn Leu Pro Leu Pro Gly Gly Val Val Pro
 115 120 125

Arg Met Leu Ile Thr Ile Leu Gly Thr Val Lys Pro Asn Ala Asn Arg
 130 135 140

Ile Ala Leu Asp Phe Gln Arg Gly Asn Asp Val Ala Phe His Phe Asn
 145 150 155 160

Pro Arg Phe Asn Glu Asn Asn Arg Arg Val Ile Val Cys Asn Thr Lys
 165 170 175

Leu Asp Asn Asn Trp Gly Arg Glu Glu Arg Gln Ser Val Phe Pro Phe
 180 185 190

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Glu Ser Gly Lys Pro Phe Lys Ile Gln Val Leu Val Glu Pro Asp His
 195 200 205

Phe Lys Val Ala Val Asn Asp Ala His Leu Leu Gln Tyr Asn His Arg
 210 215 220

Val Lys Lys Leu Asn Glu Ile Ser Lys Leu Gly Ile Ser Gly Asp Ile
 225 230 235 240

Asp Leu Thr Ser Ala Ser Tyr Thr Met Ile
 245 250

<210> 120

<211> 545

<212> PRT

<213> Homo sapiens

<400> 120

Met Asp Trp Gly Thr Glu Leu Trp Asp Gln Phe Glu Val Leu Glu Arg
 1 5 10 15

His Thr Gln Trp Gly Leu Asp Leu Leu Asp Arg Tyr Val Lys Phe Val
 20 25 30

Lys Glu Arg Thr Glu Val Glu Gln Ala Tyr Ala Lys Gln Leu Arg Ser
 35 40 45

Leu Val Lys Lys Tyr Leu Pro Lys Arg Pro Ala Lys Asp Asp Pro Glu
 50 55 60

Ser Lys Phe Ser Gln Gln Gln Ser Phe Val Gln Ile Leu Gln Glu Val
 65 70 75 80

Asn Asp Phe Ala Gly Gln Arg Glu Leu Val Ala Glu Asn Leu Ser Val
 85 90 95

Arg Val Cys Leu Glu Leu Thr Lys Tyr Ser Gln Glu Met Lys Gln Glu
 100 105 110

Arg Lys Met His Phe Gln Glu Gly Arg Arg Ala Gln Gln Gln Leu Glu
 115 120 125

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Asn Gly Phe Lys Gln Leu Glu Asn Ser Lys Arg Lys Phe Glu Arg Asp
 130 135 140

Cys Arg Glu Ala Glu Lys Ala Ala Gln Thr Ala Glu Arg Leu Asp Gln
 145 150 155 160

Asp Ile Asn Ala Thr Lys Ala Asp Val Glu Lys Ala Lys Gln Gln Ala
 165 170 175

His Leu Arg Ser His Met Ala Glu Glu Ser Lys Asn Glu Tyr Ala Ala
 180 185 190

Gln Leu Gln Arg Phe Asn Arg Asp Gln Ala His Phe Tyr Phe Ser Gln
 195 200 205

Met Pro Gln Ile Phe Asp Lys Leu Gln Asp Met Asp Glu Arg Arg Ala
 210 215 220

Thr Arg Leu Gly Ala Gly Tyr Gly Leu Leu Ser Glu Ala Glu Leu Glu
 225 230 235 240

Val Val Pro Ile Ile Ala Lys Cys Leu Glu Gly Met Lys Val Ala Ala
 245 250 255

Asn Ala Val Asp Pro Lys Asn Asp Ser His Val Leu Ile Glu Leu His
 260 265 270

Lys Ser Gly Phe Ala Arg Pro Gly Asp Val Glu Phe Glu Asp Phe Ser
 275 280 285

Gln Pro Met Asn Arg Ala Pro Ser Asp Ser Ser Leu Gly Thr Pro Ser
 290 295 300

Asp Gly Arg Pro Glu Leu Arg Gly Pro Gly Arg Ser Arg Thr Lys Arg
 305 310 315 320

Trp Pro Phe Gly Lys Lys Asn Lys Thr Val Val Thr Glu Asp Phe Ser
 325 330 335

His Leu Pro Pro Glu Gln Gln Arg Lys Arg Leu Gln Gln Gln Leu Glu
 340 345 350

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Glu Arg Ser Arg Glu Leu Gln Lys Glu Val Asp Gln Arg Glu Ala Leu
 355 360 365

Lys Lys Met Lys Asp Val Tyr Glu Lys Thr Pro Gln Met Gly Asp Pro
 370 375 380

Ala Ser Leu Glu Pro Gln Ile Ala Glu Thr Leu Ser Asn Ile Glu Arg
 385 390 395 400

Leu Lys Leu Glu Val Gln Lys Tyr Glu Ala Trp Leu Ala Glu Ala Glu
 405 410 415

Ser Arg Val Leu Ser Asn Arg Gly Asp Ser Leu Ser Arg His Ala Arg
 420 425 430

Pro Pro Asp Pro Pro Ala Ser Ala Pro Pro Asp Ser Ser Ser Asn Ser
 435 440 445

Ala Ser Gln Asp Thr Lys Glu Ser Ser Glu Glu Pro Pro Ser Glu Glu
 450 455 460

Ser Gln Asp Thr Pro Ile Tyr Thr Glu Phe Asp Glu Asp Phe Glu Glu
 465 470 475 480

Glu Pro Thr Ser Pro Ile Gly His Cys Val Ala Ile Tyr His Phe Glu
 485 490 495

Gly Ser Ser Glu Gly Thr Ile Ser Met Ala Glu Gly Glu Asp Leu Ser
 500 505 510

Leu Met Glu Glu Asp Lys Gly Asp Gly Trp Thr Arg Val Arg Arg Lys
 515 520 525

Glu Gly Gly Glu Gly Tyr Val Pro Thr Ser Tyr Leu Arg Val Thr Leu
 530 535 540

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Asn
545

<210> 121

<211> 381

<212> PRT

<213> Homo sapiens

<220>

<221> MISC_FEATURE

<222> (59) .. (59)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (300) .. (300)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (318) .. (318)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (330) .. (330)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

- 250 -

<222> (345) .. (345)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (352) .. (352)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (367) .. (367)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (369) .. (369)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (376) .. (376)

<223> Xaa=any amino acid

<220>

<221> MISC_FEATURE

<222> (378) .. (378)

<223> Xaa=any amino acid

<400> 121

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Met Trp Arg Ser Leu Gly Leu Ala Leu Ala Leu Cys Leu Leu Pro Ser
 1 5 10 15

Gly Gly Thr Glu Ser Gln Asp Gln Ser Ser Leu Cys Lys Gln Pro Pro
 20 25 30

Ala Trp Ser Ile Arg Asp Gln Asp Pro Met Leu Asn Ser Asn Gly Ser
 35 40 45

Val Thr Val Val Ala Leu Leu Gln Ala Ser Xaa Tyr Leu Cys Ile Ile
 50 55 60

Glu Ala Ser Lys Leu Glu Asp Leu Arg Val Lys Leu Lys Lys Glu Gly
 65 70 75 80

Tyr Ser Asn Ile Ser Tyr Ile Val Val Asn His Gln Gly Ile Ser Ser
 85 90 95

Arg Leu Lys Tyr Thr His Leu Lys Asn Lys Val Ser Glu His Ile Pro
 100 105 110

Val Tyr Gln Gln Glu Glu Asn Gln Thr Asp Val Trp Thr Leu Leu Asn
 115 120 125

Gly Ser Lys Asp Asp Phe Leu Ile Tyr Asp Arg Cys Gly Arg Leu Val
 130 135 140

Tyr His Leu Gly Leu Pro Phe Ser Phe Leu Thr Phe Pro Tyr Val Glu
 145 150 155 160

Glu Ala Ile Lys Ile Ala Tyr Cys Glu Lys Lys Cys Gly Asn Cys Ser
 165 170 175

Leu Thr Thr Leu Lys Asp Glu Asp Phe Cys Lys Arg Val Ser Leu Ala
 180 185 190

Thr Val Asp Lys Thr Val Glu Thr Pro Ser Pro His Tyr His His Glu
 195 200 205

His His His Asn His Gly His Gln His Leu Gly Ser Ser Glu Leu Ser
 210 215 220

Glu Asn Gln Gln Pro Gly Ala Pro Asn Ala Pro Thr His Pro Ala Pro
 225 230 235 240

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Pro Gly Leu His His His Lys His Lys Gly Gln His Arg Gln Gly
245 250 255

His Pro Glu Asn Arg Asp Met Pro Ala Ser Glu Asp Leu Gln Asp Leu
260 265 270

Gln Lys Lys Leu Cys Arg Lys Arg Cys Ile Asn Gln Leu Leu Cys Lys
275 280 285

Leu Pro Thr Asp Ser Glu Leu Ala Pro Arg Ser Xaa Cys Cys His Cys
290 295 300

Arg His Leu Ile Phe Glu Lys Thr Gly Ser Ala Ile Thr Xaa Gln Cys
305 310 315 320

Lys Glu Asn Leu Pro Ser Leu Cys Ser Xaa Gln Gly Leu Arg Ala Glu
325 330 335

Glu Asn Ile Thr Glu Ser Cys Gln Xaa Arg Leu Pro Pro Ala Ala Xaa
340 345 350

Gln Ile Ser Gln Gln Leu Ile Pro Thr Glu Ala Ser Ala Ser Xaa Arg
355 360 365

Xaa Lys Asn Gln Ala Lys Lys Xaa Glu Xaa Pro Ser Asn
370 375 380

<210> 122

<211> 912

<212> PRT

<213> Homo sapiens

<400> 122

Met Val Asp Tyr His Ala Ala Asn Gln Ser Tyr Gln Tyr Gly Pro Ser
1 5 10 15

Ser Ala Ala Met Ala Trp Arg Arg Gly Ser Met Gly Asp Tyr Met Ala
20 25 30

Gln Glu Asp Asp Trp Asp Arg Asp Leu Leu Leu Asp Pro Ala Trp Glu

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35		40		45											
Lys	Gln	Gln	Arg	Lys	Thr	Phe	Thr	Ala	Trp	Ser	Asn	Ser	His	Leu	Arg
50						55					60				
Lys	Ala	Gly	Thr	Gln	Ile	Glu	Asn	Ile	Asp	Glu	Asp	Phe	Arg	Asp	Gly
65				70					75						80
Leu	Lys	Leu	Met	Leu	Leu	Leu	Glu	Val	Ile	Ser	Gly	Glu	Arg	Leu	Pro
			85						90						95
Lys	Pro	Glu	Arg	Gly	Lys	Met	Arg	Val	His	Lys	Ile	Asn	Asn	Val	Asn
			100					105						110	
Lys	Ala	Leu	Asp	Phe	Ile	Ala	Ser	Lys	Gly	Ile	Lys	Leu	Asp	Phe	His
	115						120					125			
Arg	Ala	Glu	Glu	Ile	Val	Asp	Gly	Asn	Ala	Lys	Met	Thr	Leu	Gly	Met
	130					135						140			
Ile	Trp	Thr	Ile	Ile	Leu	Arg	Phe	Ala	Ile	Gln	Asp	Ile	Ser	Val	Glu
145					150					155					160
Glu	Thr	Ser	Ala	Lys	Glu	Gly	Leu	Leu	Leu	Trp	Cys	Gln	Arg	Lys	Thr
				165					170					175	
Ala	Pro	Tyr	Lys	Asn	Val	Asn	Val	Gln	Asn	Phe	His	Ile	Ser	Trp	Lys
			180					185						190	
Asp	Gly	Leu	Ala	Phe	Asn	Ala	Leu	Ile	His	Arg	His	Arg	Pro	Glu	Leu
	195						200					205			
Ile	Glu	Tyr	Asp	Lys	Leu	Arg	Lys	Asp	Asp	Pro	Val	Thr	Asn	Leu	Asn
210						215					220				
Asn	Ala	Phe	Glu	Val	Ala	Glu	Lys	Tyr	Leu	Asp	Ile	Pro	Lys	Met	Leu
225					230					235					240
Asp	Ala	Glu	Asp	Ile	Val	Asn	Thr	Ala	Arg	Pro	Asp	Glu	Lys	Ala	Ile
				245					250					255	
Met	Thr	Tyr	Val	Ser	Ser	Phe	Tyr	His	Ala	Phe	Ser	Gly	Ala	Gln	Lys
			260					265						270	

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Ala Glu Thr Glu Thr Ala Ala Asn Arg Ile Cys Lys Val Leu Ala Val
 275 280 285

Asn Gln Glu Asn Cys Ser Thr Ser Met Glu Asp Tyr Glu Lys Leu Ala
 290 295 300

Ser Asp Leu Leu Glu Trp Ile Arg Arg Thr Ile Pro Trp Leu Glu Asp
 305 310 315 320

Arg Val Pro Gln Lys Thr Ile Gln Glu Met Gln Gln Lys Leu Glu Asp
 325 330 335

Phe Arg Asp Tyr Arg Arg Val His Lys Pro Pro Lys Val Gln Glu Lys
 340 345 350

Cys Gln Leu Glu Ile Asn Phe Asn Ser Val Gln Thr Lys Leu Arg Leu
 355 360 365

Ser Asn Arg Pro Ala Phe Met Pro Ser Glu Gly Lys Met Val Ser Asp
 370 375 380

Ile Asn Asn Gly Trp Gln His Leu Glu Gln Ala Glu Lys Gly Tyr Glu
 385 390 395 400

Glu Trp Leu Leu Asn Glu Ile Arg Arg Leu Glu Arg Leu Asp His Leu
 405 410 415

Ala Glu Lys Phe Arg Gln Lys Ala Ser Ile His Glu Ala Trp Thr Asp
 420 425 430

Gly Lys Glu Ala Met Leu Lys His Arg Asp Tyr Glu Thr Ala Thr Leu
 435 440 445

Ser Asp Ile Lys Ala Leu Ile Arg Lys His Glu Ala Phe Glu Ser Asp
 450 455 460

Leu Ala Ala His Gln Asp Arg Val Glu Gln Ile Ala Ala Ser Ala Gln
 465 470 475 480

Glu Leu Asn Glu Leu Asp Tyr Tyr Asp Ser His Asn Val Asn Thr Arg
 485 490 495

Cys Gln Lys Ile Cys Asp Gln Trp Asp Ala Leu Gly Ser Leu Thr His
 500 505 510

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Ser Arg Arg Glu Ala Leu Glu Lys Thr Glu Lys Gln Leu Glu Ala Ile
 515 520 525

Ile Asp Gln Leu His Leu Glu Tyr Ala Lys Pro Ala Ala Pro Phe Asn
 530 535 540

Asn Trp Met Glu Ser Ala Met Glu Asp Leu Gln Asp Met Phe Ile Val
 545 550 555 560

His Thr Ile Glu Glu Ile Glu Gly Leu Ile Ser Ala His Asp Gln Phe
 565 570 575

Lys Ser Thr Leu Pro Asp Ala Asp Arg Glu Arg Glu Ala Ile Leu His
 580 585 590

Pro Gln Gly Gly Gln Arg Ile Ala Glu Ser Asn His Ile Lys Leu Ser
 595 600 605

Gly Ser Asn Pro Tyr Thr Thr Val Thr Pro Gln Ile Ile Asn Ser Lys
 610 615 620

Trp Glu Lys Val Gln Gln Leu Val Pro Lys Arg Asp His Ala Leu Leu
 625 630 635 640

Glu Glu Gln Ser Lys Gln Gln Gln Ser Asn Glu His Leu Arg Arg Gln
 645 650 655

Phe Ala Ser Gln Ala Asn Val Val Gly Pro Trp Ile Gln Thr Lys Met
 660 665 670

Glu Glu Ile Ala Ile Ser Ile Glu Met Asn Gly Thr Leu Glu Asp Gln
 675 680 685

Leu Ser His Leu Lys Gln Tyr Glu Arg Ser Ile Val Asp Tyr Lys Pro
 690 695 700

Asn Leu Asp Leu Leu Glu Gln Gln His Gln Leu Ile Gln Glu Ala Leu
 705 710 715 720

Ile Phe Asp Asn Lys His Thr Asn Tyr Thr Met Glu His Ile Arg Val
 725 730 735

Gly Trp Glu Gln Leu Leu Thr Thr Ile Ala Arg Thr Ile Asn Glu Val
 740 745 750

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Glu Asn Gln Ile Leu Thr Arg Asp Ala Lys Gly Ile Ser Gln Glu Gln
 755 760 765

Met Gln Glu Phe Arg Ala Ser Phe Asn His Phe Asp Lys Asp His Gly
 770 775 780

Gly Ala Leu Gly Arg Gly Val Gln Gly Leu Pro His Gln Pro Gly Leu
 785 790 795 800

Arg Arg Gly Glu Arg Pro Ala Gly Glu Ala Glu Phe Asn Arg Ile Met
 805 810 815

Ser Leu Val Asp Pro Asn His Ser Gly Leu Val Thr Phe Gln Ala Phe
 820 825 830

Ile Asp Phe Met Ser Arg Glu Thr Thr Asp Thr Asp Thr Ala Asp Gln
 835 840 845

Val Ile Thr Ser Phe Lys Val Leu Ala Gly Asp Lys Asn Phe Ile Thr
 850 855 860

Ala Glu Glu Leu Arg Arg Glu Leu Pro Pro Asp Gln Ala Glu Tyr Cys
 865 870 875 880

Ile Ala Arg Met Ala Pro Tyr Gln Gly Pro Asp Gly Val Arg Gly Ala
 885 890 895

Leu Asp Tyr Lys Ser Phe Ser Thr Ala Leu Tyr Gly Glu Ser Asp Leu
 900 905 910

<210> 123

<211> 407

<212> PRT

<213> Homo sapiens

<400> 123

Phe Cys Pro Ala Val Leu Cys His Pro Asn Ser Pro Leu Asp Glu Glu
 1 5 10 15

Asn Leu Thr Gln Glu Asn Gln Asp Arg Gly Thr His Val Asp Leu Gly

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20					25					30					
Leu	Ala	Ser	Ala	Asn	Val	Asp	Phe	Ala	Phe	Ser	Leu	Tyr	Lys	Gln	Leu
	35						40					45			
Val	Leu	Lys	Ala	Pro	Asp	Lys	Asn	Val	Ile	Phe	Ser	Pro	Leu	Ser	Ile
	50					55					60				
Ser	Thr	Ala	Leu	Ala	Phe	Leu	Ser	Leu	Gly	Ala	His	Asn	Thr	Thr	Leu
	65					70					75				80
Thr	Glu	Ile	Leu	Lys	Gly	Leu	Lys	Phe	Asn	Leu	Thr	Glu	Thr	Ser	Glu
				85					90					95	
Ala	Glu	Ile	His	Gln	Ser	Phe	Gln	His	Leu	Leu	Arg	Thr	Leu	Asn	Gln
			100					105						110	
Ser	Ser	Asp	Glu	Leu	Gln	Leu	Ser	Met	Gly	Asn	Ala	Met	Phe	Val	Lys
		115					120					125			
Glu	Gln	Leu	Ser	Leu	Leu	Asp	Arg	Phe	Thr	Glu	Asp	Ala	Lys	Arg	Leu
	130					135					140				
Tyr	Gly	Ser	Glu	Ala	Phe	Ala	Thr	Asp	Phe	Gln	Asp	Ser	Ala	Ala	Ala
	145					150					155				160
Lys	Lys	Leu	Ile	Asn	Asp	Tyr	Val	Lys	Asn	Gly	Thr	Arg	Gly	Lys	Ile
				165					170					175	
Thr	Asp	Leu	Ile	Lys	Asp	Leu	Asp	Ser	Gln	Thr	Met	Met	Val	Leu	Val
				180				185					190		
Asn	Tyr	Ile	Phe	Phe	Lys	Ala	Lys	Trp	Glu	Met	Pro	Phe	Asp	Pro	Gln
		195					200					205			
Asp	Thr	His	Gln	Ser	Arg	Phe	Tyr	Leu	Ser	Lys	Lys	Lys	Trp	Val	Met
	210					215					220				
Val	Pro	Met	Met	Ser	Leu	His	His	Leu	Thr	Ile	Pro	Tyr	Phe	Arg	Asp
	225					230					235				240
Glu	Glu	Leu	Ser	Cys	Thr	Val	Val	Glu	Leu	Lys	Tyr	Thr	Gly	Asn	Ala
				245					250					255	

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Ser Ala Leu Phe Ile Leu Pro Asp Gln Asp Lys Met Glu Glu Val Glu
 260 265 270

Ala Met Leu Leu Pro Glu Thr Leu Lys Arg Trp Arg Asp Ser Leu Glu
 275 280 285

Phe Arg Glu Ile Gly Glu Leu Tyr Leu Pro Lys Phe Ser Ile Ser Arg
 290 295 300

Asp Tyr Asn Leu Asn Asp Ile Leu Leu Gln Leu Gly Ile Glu Glu Ala
 305 310 315 320

Phe Thr Ser Lys Ala Asp Leu Ser Gly Ile Thr Gly Ala Arg Asn Leu
 325 330 335

Ala Val Ser Gln Val Val His Lys Ala Val Leu Asp Val Phe Glu Glu
 340 345 350

Gly Thr Glu Ala Ser Ala Ala Thr Ala Val Lys Ile Thr Leu Leu Ser
 355 360 365

Ala Leu Val Glu Thr Arg Thr Ile Val Arg Phe Asn Arg Pro Phe Leu
 370 375 380

Met Ile Ile Val Pro Thr Asp Thr Gln Asn Ile Phe Phe Met Ser Lys
 385 390 395 400

Val Thr Asn Pro Lys Gln Ala
 405

<210> 124

<211> 451

<212> PRT

<213> Homo sapiens

<400> 124

Met Gly Lys Ser Phe Ala Asn Phe Met Cys Lys Lys Asp Phe His Pro
 1 5 10 15

Ala Ser Lys Ser Asn Ile Lys Lys Val Trp Met Ala Glu Gln Lys Ile
 20 25 30

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Ser Tyr Asp Lys Lys Lys Gln Glu Glu Leu Met Gln Gln Tyr Leu Lys
 35 40 45

Glu Gln Glu Ser Tyr Asp Asn Arg Leu Leu Met Gly Asp Glu Arg Val
 50 55 60

Lys Asn Gly Leu Asn Phe Met Tyr Glu Ala Pro Pro Gly Ala Lys Lys
 65 70 75 80

Glu Asn Lys Glu Lys Glu Glu Thr Glu Gly Glu Thr Glu Tyr Lys Phe
 85 90 95

Glu Trp Gln Lys Gly Ala Pro Arg Glu Lys Tyr Ala Lys Asp Asp Met
 100 105 110

Asn Ile Arg Asp Gln Pro Phe Gly Ile Gln Val Arg Asn Val Arg Cys
 115 120 125

Ile Lys Cys His Lys Trp Val Met Ser Thr Gln Ile Glu Asn Val Leu
 130 135 140

Cys Leu Val Phe Leu Glu Val Asn Ala Ser Ser Val Pro Thr Asp Gly
 145 150 155 160

Ser Gly Pro Ser Met His Pro Ser Glu Leu Ile Gly Glu Met Arg Asn
 165 170 175

Gln Trp Val Cys Thr Glu Thr Lys Cys Thr Gly Glu Lys Leu Asp Arg
 180 185 190

Lys Leu Ile His His Arg Ser Met Leu Gln Val Gln Gly Glu Glu Asp
 195 200 205

Pro Glu Val Glu Phe Leu Lys Ser Leu Thr Thr Lys Gln Lys Gln Lys
 210 215 220

Leu Leu Arg Lys Leu Asp Arg Leu Glu Lys Lys Lys Lys Lys Lys Asp
 225 230 235 240

Arg Lys Lys Lys Lys Phe Gln Lys Ser Arg Ser Lys His Lys Lys His
 245 250 255

Lys Ser Ser Ser Ser Tyr Leu Pro Pro Pro Pro Pro Leu Pro Leu Leu
 260 265 270

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Arg Leu Gln Lys Ala Val Val Arg Val Arg Val Thr Ile Lys Lys Lys
 275 280 285

Lys Leu Gln Arg Lys Lys Arg Lys Lys Asn Lys Cys Ser Gly His Asn
 290 295 300

Asn Ser Asp Ser Glu Glu Lys Asp Lys Ser Lys Lys Arg Lys Leu His
 305 310 315 320

Glu Glu Leu Ser Ser Thr His His Asn Arg Glu Lys Ala Lys Glu Lys
 325 330 335

Pro Arg Phe Leu Lys His Glu Ser Ser Arg Glu Asp Ser Lys Trp Ser
 340 345 350

His Ser Asp Ser Asp Lys Lys Ser Arg Thr His Lys His Ser Pro Glu
 355 360 365

Lys Arg Gly Ser Glu Arg Lys Glu Gly Ser Ser Arg Ser His Gly Arg
 370 375 380

Glu Glu Arg Ser Arg Arg Ser Gln Pro Glu Val Leu Val Val Thr Ser
 385 390 395 400

Lys Gly Arg Gln Gly Asn Gly His Ser Glu His Pro Gly Glu Glu Gln
 405 410 415

Ser Arg Arg Asn Asp Ser Arg Ser His Gly Thr Asp Leu Tyr Arg Gly
 420 425 430

Glu Lys Met Tyr Arg Glu His Pro Gly Gly Thr His Thr Lys Val Thr
 435 440 445

Gln Arg Glu
 450

<210> 125

<211> 658

<212> PRT

<213> Homo sapiens

- 261 -

<400> 125

Met Ala Glu Ala Ala Ala Ala Gly Gly Thr Gly Leu Gly Ala Gly
 1 5 10 15

Ala Ser Tyr Gly Ser Ala Ala Asp Arg Asp Arg Asp Pro Asp Pro Asp
 20 25 30

Arg Ala Gly Arg Arg Leu Arg Val Leu Ser Gly His Leu Leu Gly Arg
 35 40 45

Pro Arg Glu Ala Leu Ser Thr Asn Glu Cys Lys Ala Arg Arg Ala Ala
 50 55 60

Ser Ala Ala Thr Ala Ala Pro Thr Ala Thr Pro Ala Ala Gln Glu Ser
 65 70 75 80

Gly Thr Ile Pro Lys Lys Arg Gln Glu Val Met Lys Trp Asn Gly Trp
 85 90 95

Gly Tyr Asn Asp Ser Lys Phe Ile Phe Asn Lys Lys Gly Gln Ile Glu
 100 105 110

Leu Thr Gly Lys Arg Tyr Pro Leu Ser Gly Met Gly Leu Pro Thr Phe
 115 120 125

Lys Glu Trp Ile Gln Asn Thr Leu Gly Val Asn Val Glu His Lys Thr
 130 135 140

Thr Ser Lys Ala Ser Leu Asn Pro Ser Asp Thr Pro Pro Ser Val Val
 145 150 155 160

Asn Glu Asp Phe Leu His Asp Leu Lys Glu Thr Asn Ile Ser Tyr Ser
 165 170 175

Gln Glu Ala Asp Asp Arg Val Phe Arg Ala His Gly His Cys Leu His
 180 185 190

Glu Ile Phe Leu Leu Arg Glu Gly Met Phe Glu Arg Ile Pro Asp Ile
 195 200 205

Val Leu Trp Pro Thr Cys His Asp Asp Val Val Lys Ile Val Asn Leu
 210 215 220

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Ala Cys Lys Tyr Asn Leu Cys Ile Ile Pro Ile Gly Gly Gly Thr Ser
 225 230 235 240

Val Ser Tyr Gly Leu Met Cys Pro Ala Asp Glu Thr Arg Thr Ile Ile
 245 250 255

Ser Leu Asp Thr Ser Gln Met Asn Arg Ile Leu Trp Val Asp Glu Asn
 260 265 270

Asn Leu Thr Ala His Val Glu Ala Gly Ile Thr Gly Gln Glu Leu Glu
 275 280 285

Arg Gln Leu Lys Glu Ser Gly Tyr Cys Thr Gly His Glu Pro Asp Ser
 290 295 300

Leu Glu Phe Ser Thr Val Gly Gly Trp Val Ser Thr Arg Ala Ser Gly
 305 310 315 320

Met Lys Lys Asn Ile Tyr Gly Asn Ile Glu Asp Leu Val Val His Ile
 325 330 335

Lys Met Val Thr Pro Arg Gly Ile Ile Glu Lys Ser Cys Gln Gly Pro
 340 345 350

Arg Met Ser Thr Gly Pro Asp Ile His His Phe Ile Met Gly Ser Glu
 355 360 365

Gly Thr Leu Gly Val Ile Thr Glu Ala Thr Ile Lys Ile Arg Pro Val
 370 375 380

Pro Glu Tyr Gln Lys Tyr Gly Ser Val Ala Phe Pro Asn Phe Glu Gln
 385 390 395 400

Gly Val Ala Cys Leu Arg Glu Ile Ala Lys Gln Arg Cys Ala Pro Ala
 405 410 415

Ser Ile Arg Leu Met Asp Asn Lys Gln Phe Gln Phe Gly His Ala Leu
 420 425 430

Lys Pro Gln Val Ser Ser Ile Phe Thr Ser Phe Leu Asp Gly Leu Lys
 435 440 445

Lys Phe Tyr Ile Thr Lys Phe Lys Gly Phe Asp Pro Asn Gln Leu Ser
 450 455 460

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Val Ala Thr Leu Leu Phe Glu Gly Asp Arg Glu Lys Val Leu Gln His
 465 470 475 480

Glu Lys Gln Val Tyr Asp Ile Ala Ala Lys Phe Gly Gly Leu Ala Ala
 485 490 495

Gly Glu Asp Asn Gly Gln Arg Gly Tyr Leu Leu Thr Tyr Val Ile Ala
 500 505 510

Tyr Ile Arg Asp Leu Ala Leu Glu Tyr Tyr Val Leu Gly Glu Ser Phe
 515 520 525

Glu Thr Ser Ala Pro Trp Asp Arg Val Val Asp Leu Cys Arg Asn Val
 530 535 540

Lys Glu Arg Ile Thr Arg Glu Cys Lys Glu Lys Gly Val Gln Phe Ala
 545 550 555 560

Pro Phe Ser Thr Cys Arg Val Thr Gln Thr Tyr Asp Ala Gly Ala Cys
 565 570 575

Ile Tyr Phe Tyr Phe Ala Phe Asn Tyr Arg Gly Ile Ser Asp Pro Leu
 580 585 590

Thr Val Phe Glu Gln Thr Glu Ala Ala Ala Arg Glu Glu Ile Leu Ala
 595 600 605

Asn Gly Gly Ser Leu Ser His His His Gly Val Gly Lys Leu Arg Lys
 610 615 620

Gln Trp Leu Lys Glu Ser Ile Ser Asp Val Gly Phe Gly Met Leu Lys
 625 630 635 640

Ser Val Lys Glu Tyr Val Asp Pro Asn Asn Ile Phe Gly Asn Arg Asn
 645 650 655

Leu Leu

<210> 126

<211> 530

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<212> PRT

<213> Homo sapiens

<400> 126

Met Arg Arg Leu Trp Gly Ala Ala Arg Lys Pro Ser Gly Ala Gly Trp
 1 5 10 15

Glu Lys Glu Trp Ala Glu Ala Pro Gln Glu Ala Pro Gly Ala Trp Ser
 20 25 30

Gly Arg Leu Gly Pro Gly Arg Ser Gly Arg Lys Gly Arg Ala Val Pro
 35 40 45

Gly Trp Ala Ser Trp Pro Ala His Leu Ala Leu Ala Ala Arg Pro Ala
 50 55 60

Arg His Leu Gly Gly Ala Gly Gln Gly Pro Arg Pro Leu His Ser Gly
 65 70 75 80

Thr Ala Pro Phe His Ser Arg Ala Ser Gly Glu Arg Gln Arg Arg Leu
 85 90 95

Glu Pro Gln Leu Gln His Glu Ser Arg Cys Arg Ser Ser Thr Pro Ala
 100 105 110

Asp Ala Trp Arg Ala Glu Ala Ala Leu Pro Val Arg Ala Met Gly Ala
 115 120 125

Pro Trp Gly Ser Pro Thr Ala Ala Ala Gly Gly Arg Arg Gly Trp Arg
 130 135 140

Arg Gly Arg Gly Leu Pro Trp Thr Val Cys Val Leu Ala Ala Ala Gly
 145 150 155 160

Leu Thr Cys Thr Ala Leu Ile Thr Tyr Ala Cys Trp Gly Gln Leu Pro
 165 170 175

Pro Leu Pro Trp Ala Ser Pro Thr Pro Ser Arg Pro Val Gly Val Leu
 180 185 190

Leu Trp Trp Glu Pro Phe Gly Gly Arg Asp Ser Ala Pro Arg Pro Pro
 195 200 205

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Pro Asp Cys Arg Leu Arg Phe Asn Ile Ser Gly Cys Arg Leu Leu Thr
 210 215 220

Asp Arg Ala Ser Tyr Gly Glu Ala Gln Ala Val Leu Phe His His Arg
 225 230 235 240

Asp Leu Val Lys Gly Pro Pro Asp Trp Pro Pro Pro Trp Gly Ile Gln
 245 250 255

Ala His Thr Ala Glu Glu Val Asp Leu Arg Val Leu Asp Tyr Glu Glu
 260 265 270

Ala Ala Ala Ala Glu Ala Leu Ala Thr Ser Ser Pro Arg Pro Pro
 275 280 285

Gly Gln Arg Trp Val Trp Met Asn Phe Glu Ser Pro Ser His Ser Pro
 290 295 300

Gly Leu Arg Ser Leu Ala Ser Asn Leu Phe Asn Trp Thr Leu Ser Tyr
 305 310 315 320

Arg Ala Asp Ser Asp Val Phe Val Pro Tyr Gly Tyr Leu Tyr Pro Arg
 325 330 335

Ser His Pro Gly Asp Pro Pro Ser Gly Leu Ala Pro Pro Leu Ser Arg
 340 345 350

Lys Gln Gly Leu Val Ala Trp Val Val Ser His Trp Asp Glu Arg Gln
 355 360 365

Ala Arg Val Arg Tyr Tyr His Gln Leu Ser Gln His Val Thr Val Asp
 370 375 380

Val Phe Gly Arg Gly Gly Pro Gly Gln Pro Val Pro Glu Ile Gly Leu
 385 390 395 400

Leu His Thr Val Ala Arg Tyr Lys Phe Tyr Leu Ala Phe Glu Asn Ser
 405 410 415

Gln His Leu Asp Tyr Ile Thr Glu Lys Leu Trp Arg Asn Ala Leu Leu
 420 425 430

Ala Gly Ala Val Pro Val Val Leu Gly Pro Asp Arg Ala Asn Tyr Glu
 435 440 445

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Arg Phe Val Pro Arg Gly Ala Phe Ile His Val Asp Asp Phe Pro Ser
 450 455 460

Ala Ser Ser Leu Ala Ser Tyr Leu Leu Phe Leu Asp Arg Asn Pro Ala
 465 470 475 480

Val Tyr Arg Arg Tyr Phe His Trp Arg Arg Ser Tyr Ala Val His Ile
 485 490 495

Thr Ser Phe Trp Asp Glu Pro Trp Cys Arg Val Cys Gln Ala Val Gln
 500 505 510

Arg Ala Gly Asp Arg Pro Lys Ser Ile Arg Asn Leu Ala Ser Trp Phe
 515 520 525

Glu Arg
 530

<210> 127

<211> 541

<212> PRT

<213> Homo sapiens

<400> 127

Met Lys Ser Tyr Thr Pro Tyr Phe Ile Leu Leu Trp Ser Ala Val Gly
 1 5 10 15

Ile Ala Lys Ala Ala Lys Ile Ile Ile Val Pro Pro Ile Met Phe Glu
 20 25 30

Ser His Met Tyr Ile Phe Lys Thr Leu Ala Ser Ala Leu His Glu Arg
 35 40 45

Gly His His Thr Val Phe Leu Leu Ser Glu Gly Arg Asp Ile Ala Pro
 50 55 60

Ser Asn His Tyr Ser Leu Gln Arg Tyr Pro Gly Ile Phe Asn Ser Thr
 65 70 75 80

Thr Ser Asp Ala Phe Leu Gln Ser Lys Met Arg Asn Ile Phe Ser Gly

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85								90				95						
Arg	Leu	Thr	Ala	Ile	Glu	Leu	Phe	Asp	Ile	Leu	Asp	His	Tyr	Thr	Lys			
			100					105					110					
Asn	Cys	Asp	Leu	Met	Val	Gly	Asn	His	Ala	Leu	Ile	Gln	Gly	Leu	Lys			
		115					120					125						
Lys	Glu	Lys	Phe	Asp	Leu	Leu	Leu	Val	Asp	Pro	Asn	Asp	Met	Cys	Gly			
	130					135					140							
Phe	Val	Ile	Ala	His	Leu	Leu	Gly	Val	Lys	Tyr	Ala	Val	Phe	Ser	Thr			
145					150					155					160			
Gly	Leu	Trp	Tyr	Pro	Ala	Glu	Val	Gly	Ala	Pro	Ala	Pro	Leu	Ala	Tyr			
				165					170					175				
Val	Pro	Glu	Phe	Asn	Ser	Leu	Leu	Thr	Asp	Arg	Met	Asn	Leu	Leu	Gln			
			180					185					190					
Arg	Met	Lys	Asn	Thr	Gly	Val	Tyr	Leu	Ile	Ser	Arg	Leu	Gly	Val	Ser			
		195					200					205						
Phe	Leu	Val	Leu	Pro	Lys	Tyr	Glu	Arg	Ile	Met	Gln	Lys	Tyr	Asn	Leu			
	210					215					220							
Leu	Pro	Glu	Lys	Ser	Met	Tyr	Asp	Leu	Val	His	Gly	Ser	Ser	Leu	Trp			
225					230					235					240			
Met	Leu	Cys	Thr	Asp	Val	Ala	Leu	Glu	Phe	Pro	Arg	Pro	Thr	Leu	Pro			
				245					250					255				
Asn	Val	Val	Tyr	Val	Gly	Gly	Ile	Leu	Thr	Lys	Pro	Ala	Ser	Pro	Leu			
			260					265					270					
Pro	Glu	Asp	Leu	Gln	Arg	Trp	Val	Asn	Gly	Ala	Asn	Glu	His	Gly	Phe			
		275					280					285						
Val	Leu	Val	Ser	Phe	Gly	Ala	Gly	Val	Lys	Tyr	Leu	Ser	Glu	Asp	Ile			
	290					295					300							
Ala	Asn	Lys	Leu	Ala	Gly	Ala	Leu	Gly	Arg	Leu	Pro	Gln	Lys	Val	Ile			
305					310					315					320			

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Trp Arg Phe Ser Gly Pro Lys Pro Lys Asn Leu Gly Asn Asn Thr Lys
 325 330 335

Leu Ile Glu Trp Leu Pro Gln Asn Asp Leu Leu Gly His Ser Lys Ile
 340 345 350

Lys Ala Phe Leu Ser His Gly Gly Leu Asn Ser Ile Phe Glu Thr Met
 355 360 365

Tyr His Gly Val Pro Val Val Gly Ile Pro Leu Phe Gly Asp His Tyr
 370 375 380

Asp Thr Met Thr Arg Val Gln Ala Lys Gly Met Gly Ile Leu Leu Glu
 385 390 395 400

Trp Lys Thr Val Thr Glu Lys Glu Leu Tyr Glu Ala Leu Val Lys Val
 405 410 415

Ile Asn Asn Pro Ser Tyr Arg Gln Arg Ala Gln Lys Leu Ser Glu Ile
 420 425 430

His Lys Asp Gln Pro Gly His Pro Val Asn Arg Thr Ile Tyr Trp Ile
 435 440 445

Asp Tyr Ile Ile Arg His Asn Gly Ala His His Leu Arg Ala Ala Val
 450 455 460

His Gln Ile Ser Phe Cys Gln Tyr Phe Leu Leu Asp Ile Ala Phe Val
 465 470 475 480

Leu Leu Leu Gly Ala Ala Leu Leu Tyr Phe Leu Leu Ser Trp Val Thr
 485 490 495

Lys Phe Ile Tyr Arg Lys Ile Lys Ser Leu Trp Ser Arg Asn Lys His
 500 505 510

Ser Thr Val Asn Gly His Tyr His Asn Gly Ile Leu Asn Gly Lys Tyr
 515 520 525

Lys Arg Asn Gly His Ile Lys His Glu Lys Lys Val Lys
 530 535 540

<210> 128

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<211> 465

<212> PRT

<213> Homo sapiens

<400> 128

Met Ala Met Thr Gly Ser Thr Pro Cys Ser Ser Met Ser Asn His Thr
 1 5 10 15

Lys Glu Arg Val Thr Met Thr Lys Val Thr Leu Glu Asn Phe Tyr Ser
 20 25 30

Asn Leu Ile Ala Gln His Glu Glu Arg Glu Met Arg Gln Lys Lys Leu
 35 40 45

Glu Lys Val Met Glu Glu Glu Gly Leu Lys Asp Glu Glu Lys Arg Leu
 50 55 60

Arg Arg Ser Ala His Ala Arg Lys Glu Thr Glu Phe Leu Arg Leu Lys
 65 70 75 80

Arg Thr Arg Leu Gly Leu Glu Asp Phe Glu Ser Leu Lys Val Ile Gly
 85 90 95

Arg Gly Ala Phe Gly Glu Val Arg Leu Val Gln Lys Lys Asp Thr Gly
 100 105 110

His Val Tyr Ala Met Lys Ile Leu Arg Lys Ala Asp Met Leu Glu Lys
 115 120 125

Glu Gln Val Gly His Ile Arg Ala Glu Arg Asp Ile Leu Val Glu Ala
 130 135 140

Asp Ser Leu Trp Val Val Lys Met Phe Tyr Ser Phe Gln Asp Lys Leu
 145 150 155 160

Asn Leu Tyr Leu Ile Met Glu Phe Leu Pro Gly Gly Asp Met Met Thr
 165 170 175

Leu Leu Met Lys Lys Asp Thr Leu Thr Glu Glu Glu Thr Gln Phe Tyr
 180 185 190

Ile Ala Glu Thr Val Leu Ala Ile Asp Ser Ile His Gln Leu Gly Phe

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195					200					205					
Ile	His	Arg	Asp	Ile	Lys	Pro	Asp	Asn	Leu	Leu	Leu	Asp	Ser	Lys	Gly
210						215					220				
His	Val	Lys	Leu	Ser	Asp	Phe	Gly	Leu	Cys	Thr	Gly	Leu	Lys	Lys	Ala
225					230					235					240
His	Arg	Thr	Glu	Phe	Tyr	Arg	Asn	Leu	Asn	His	Ser	Leu	Pro	Ser	Asp
				245					250					255	
Phe	Thr	Phe	Gln	Asn	Met	Asn	Ser	Lys	Arg	Lys	Ala	Glu	Thr	Trp	Lys
			260					265					270		
Arg	Asn	Arg	Arg	Gln	Leu	Ala	Phe	Ser	Thr	Val	Gly	Thr	Pro	Asp	Tyr
	275						280					285			
Ile	Ala	Pro	Glu	Val	Phe	Met	Gln	Thr	Gly	Tyr	Asn	Lys	Leu	Cys	Asp
290						295					300				
Trp	Trp	Ser	Leu	Gly	Val	Ile	Met	Tyr	Glu	Met	Leu	Ile	Gly	Tyr	Pro
305					310					315					320
Pro	Phe	Cys	Ser	Glu	Thr	Pro	Gln	Glu	Thr	Tyr	Lys	Lys	Val	Met	Asn
				325					330					335	
Trp	Lys	Glu	Thr	Leu	Thr	Phe	Pro	Pro	Glu	Val	Pro	Ile	Ser	Glu	Lys
				340					345				350		
Ala	Lys	Asp	Leu	Ile	Leu	Arg	Phe	Cys	Cys	Glu	Trp	Glu	His	Arg	Ile
	355						360					365			
Gly	Ala	Pro	Gly	Val	Glu	Glu	Ile	Lys	Ser	Asn	Ser	Phe	Phe	Glu	Gly
370						375					380				
Val	Asp	Trp	Glu	His	Ile	Arg	Glu	Arg	Pro	Ala	Ala	Ile	Ser	Ile	Glu
385					390					395					400
Ile	Lys	Ser	Ile	Asp	Asp	Thr	Ser	Asn	Phe	Asp	Glu	Phe	Pro	Glu	Ser
				405					410					415	
Asp	Ile	Leu	Lys	Pro	Thr	Val	Ala	Thr	Ser	Asn	His	Pro	Glu	Thr	Asp
			420					425					430		

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Tyr Lys Asn Lys Asp Trp Val Phe Ile Asn Tyr Thr Tyr Lys Arg Phe
 435 440 445

Glu Gly Leu Thr Ala Arg Gly Ala Ile Pro Ser Tyr Met Lys Ala Ala
 450 455 460

Lys
 465

<210> 129

<211> 493

<212> PRT

<213> Homo sapiens

<400> 129

Met Ala Leu Phe Gly Ala Leu Phe Leu Ala Leu Leu Ala Gly Ala His
 1 5 10 15

Ala Glu Phe Pro Gly Cys Lys Ile Arg Val Thr Ser Lys Ala Leu Glu
 20 25 30

Leu Val Lys Gln Glu Gly Leu Arg Phe Leu Glu Gln Glu Leu Glu Thr
 35 40 45

Ile Thr Ile Pro Asp Leu Arg Gly Lys Glu Gly His Phe Tyr Tyr Asn
 50 55 60

Ile Ser Glu Val Lys Val Thr Glu Leu Gln Leu Thr Ser Ser Glu Leu
 65 70 75 80

Asp Phe Gln Pro Gln Gln Glu Leu Met Leu Gln Ile Thr Asn Ala Ser
 85 90 95

Leu Gly Leu Arg Phe Arg Arg Gln Leu Leu Tyr Trp Phe Phe Tyr Asp
 100 105 110

Gly Gly Tyr Ile Asn Ala Ser Ala Glu Gly Val Ser Ile Arg Thr Gly
 115 120 125

Leu Glu Leu Ser Arg Asp Pro Ala Gly Arg Met Lys Val Ser Asn Val
 130 135 140

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Ser Cys Gln Ala Ser Val Ser Arg Met His Ala Ala Phe Gly Gly Thr
 145 150 155 160

Phe Lys Lys Val Tyr Asp Phe Leu Ser Thr Phe Ile Thr Ser Gly Met
 165 170 175

Arg Phe Leu Leu Asn Gln Gln Ile Cys Pro Val Leu Tyr His Ala Gly
 180 185 190

Thr Val Leu Leu Asn Ser Leu Leu Asp Thr Val Pro Val Arg Ser Ser
 195 200 205

Val Asp Glu Leu Val Gly Ile Asp Tyr Ser Leu Met Lys Asp Pro Val
 210 215 220

Ala Ser Thr Ser Asn Leu Asp Met Asp Phe Arg Gly Ala Phe Phe Pro
 225 230 235 240

Leu Thr Glu Arg Asn Trp Ser Leu Pro Asn Arg Ala Val Glu Pro Gln
 245 250 255

Leu Gln Glu Glu Glu Arg Met Val Tyr Val Ala Phe Ser Glu Phe Phe
 260 265 270

Phe Asp Ser Ala Met Glu Ser Tyr Phe Arg Ala Gly Ala Leu Gln Leu
 275 280 285

Leu Leu Val Gly Asp Lys Val Pro His Asp Leu Asp Met Leu Leu Arg
 290 295 300

Ala Thr Tyr Phe Gly Ser Ile Val Leu Leu Ser Pro Ala Val Ile Asp
 305 310 315 320

Ser Pro Leu Lys Leu Glu Leu Arg Val Leu Ala Pro Pro Arg Cys Thr
 325 330 335

Ile Lys Pro Ser Gly Thr Thr Ile Ser Val Thr Ala Ser Val Thr Ile
 340 345 350

Ala Leu Val Pro Pro Asp Gln Pro Glu Val Gln Leu Ser Ser Met Thr
 355 360 365

Met Asp Ala Arg Leu Ser Ala Lys Met Ala Leu Arg Gly Lys Ala Leu
 370 375 380

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Arg Thr Gln Leu Asp Leu Arg Arg Phe Arg Ile Tyr Ser Asn His Ser
 385 390 395 400

Ala Leu Glu Ser Leu Ala Leu Ile Pro Leu Gln Ala Pro Leu Lys Thr
 405 410 415

Met Leu Gln Ile Gly Val Met Pro Met Leu Asn Glu Arg Thr Trp Arg
 420 425 430

Gly Val Gln Ile Pro Leu Pro Glu Gly Ile Asn Phe Val His Glu Val
 435 440 445

Val Thr Asn His Ala Gly Phe Leu Thr Ile Gly Ala Asp Leu His Phe
 450 455 460

Ala Lys Gly Leu Arg Glu Val Ile Glu Lys Asn Arg Pro Ala Asp Val
 465 470 475 480

Arg Ala Ser Thr Ala Pro Thr Pro Ser Thr Ala Ala Val
 485 490

<210> 130

<211> 801

<212> PRT

<213> Homo sapiens

<400> 130

Leu Pro Leu His Ala Val Glu Lys Thr Gly Arg Pro Gly Gln Pro Ala
 1 5 10 15

Leu Lys Met Pro Gly Lys Leu Arg Ser Asp Ala Gly Leu Glu Ser Asp
 20 25 30

Thr Ala Met Lys Lys Gly Glu Thr Leu Arg Lys Gln Ile Glu Glu Lys
 35 40 45

Glu Lys Lys Glu Lys Pro Lys Ser Asp Lys Thr Glu Glu Ile Ala Glu
 50 55 60

Glu Glu Glu Thr Val Phe Pro Lys Ala Lys Gln Val Lys Lys Lys Ala

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65					70						75					80
Glu	Pro	Ser	Glu	Val	Asp	Met	Asn	Ser	Pro	Lys	Ser	Lys	Lys	Ala	Lys	
				85					90					95		
Lys	Lys	Glu	Glu	Pro	Ser	Gln	Asn	Asp	Ile	Ser	Pro	Lys	Thr	Lys	Ser	
			100					105					110			
Leu	Arg	Lys	Lys	Lys	Glu	Pro	Ile	Glu	Lys	Lys	Val	Val	Ser	Ser	Lys	
		115					120					125				
Thr	Lys	Lys	Val	Thr	Lys	Asn	Glu	Glu	Pro	Ser	Glu	Glu	Glu	Ile	Asp	
	130					135					140					
Ala	Pro	Lys	Pro	Lys	Lys	Met	Lys	Lys	Glu	Lys	Glu	Met	Asn	Gly	Glu	
145						150				155					160	
Thr	Arg	Glu	Lys	Ser	Pro	Lys	Leu	Lys	Asn	Gly	Phe	Pro	His	Pro	Glu	
				165					170					175		
Pro	Asp	Cys	Asn	Pro	Ser	Glu	Ala	Ala	Ser	Glu	Glu	Ser	Asn	Ser	Glu	
			180					185					190			
Ile	Glu	Gln	Glu	Ile	Pro	Val	Glu	Gln	Lys	Glu	Gly	Ala	Phe	Ser	Asn	
		195					200					205				
Phe	Pro	Ile	Ser	Glu	Glu	Thr	Ile	Lys	Leu	Leu	Lys	Gly	Arg	Gly	Val	
	210					215					220					
Thr	Phe	Leu	Phe	Pro	Ile	Gln	Ala	Lys	Thr	Phe	His	His	Val	Tyr	Ser	
225					230					235					240	
Gly	Lys	Asp	Leu	Ile	Ala	Gln	Ala	Arg	Thr	Gly	Thr	Gly	Lys	Thr	Phe	
				245					250					255		
Ser	Phe	Ala	Ile	Pro	Leu	Ile	Glu	Lys	Leu	His	Gly	Glu	Leu	Gln	Asp	
			260					265					270			
Arg	Lys	Arg	Gly	Arg	Ala	Pro	Gln	Val	Leu	Val	Leu	Ala	Pro	Thr	Arg	
	275						280					285				
Glu	Leu	Ala	Asn	Gln	Val	Ser	Lys	Asp	Phe	Ser	Asp	Ile	Thr	Lys	Lys	
	290						295				300					

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Leu Ser Val Ala Cys Phe Tyr Gly Gly Thr Pro Tyr Gly Gly Gln Phe
 305 310 315 320

Glu Arg Met Arg Asn Gly Ile Asp Ile Leu Val Gly Thr Pro Gly Arg
 325 330 335

Ile Lys Asp His Ile Gln Asn Gly Lys Leu Asp Leu Thr Lys Leu Lys
 340 345 350

His Val Val Leu Asp Glu Val Asp Gln Met Leu Asp Met Gly Phe Ala
 355 360 365

Asp Gln Val Glu Glu Ile Leu Ser Val Ala Tyr Lys Lys Asp Ser Glu
 370 375 380

Asp Asn Pro Gln Thr Leu Leu Phe Ser Ala Thr Cys Pro His Trp Val
 385 390 395 400

Phe Asn Val Ala Lys Lys Tyr Met Lys Ser Thr Tyr Glu Gln Val Asp
 405 410 415

Leu Ile Gly Lys Lys Thr Gln Lys Thr Ala Ile Thr Val Glu His Leu
 420 425 430

Ala Ile Lys Cys His Trp Thr Gln Arg Ala Ala Val Ile Gly Asp Val
 435 440 445

Ile Arg Val Tyr Ser Gly His Gln Gly Arg Thr Ile Ile Phe Cys Glu
 450 455 460

Thr Lys Lys Glu Ala Gln Glu Leu Ser Gln Asn Ser Ala Ile Lys Gln
 465 470 475 480

Asp Ala Gln Ser Leu His Gly Asp Ile Pro Gln Lys Gln Arg Glu Ile
 485 490 495

Thr Leu Lys Gly Phe Arg Asn Gly Ser Phe Gly Val Leu Val Ala Thr
 500 505 510

Asn Val Ala Ala Arg Gly Leu Asp Ile Pro Glu Val Asp Leu Val Ile
 515 520 525

Gln Ser Ser Pro Pro Lys Asp Val Glu Ser Tyr Ile His Arg Ser Gly
 530 535 540

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Arg Thr Gly Arg Ala Gly Arg Thr Gly Val Cys Ile Cys Phe Tyr Gln
 545 550 555 560

His Lys Glu Glu Tyr Gln Leu Val Gln Val Glu Gln Lys Ala Gly Ile
 565 570 575

Lys Phe Lys Arg Ile Gly Val Pro Ser Ala Thr Glu Ile Ile Lys Ala
 580 585 590

Ser Ser Lys Asp Ala Ile Arg Leu Leu Asp Ser Val Pro Pro Thr Ala
 595 600 605

Ile Ser His Phe Lys Gln Ser Ala Glu Lys Leu Ile Glu Glu Lys Gly
 610 615 620

Ala Val Glu Ala Leu Ala Ala Ala Leu Ala His Ile Ser Gly Ala Thr
 625 630 635 640

Ser Val Asp Gln Arg Ser Leu Ile Asn Ser Asn Val Gly Phe Val Thr
 645 650 655

Met Ile Leu Gln Cys Ser Ile Glu Met Pro Asn Ile Ser Tyr Ala Trp
 660 665 670

Lys Glu Leu Lys Glu Gln Leu Gly Glu Glu Ile Asp Ser Lys Val Lys
 675 680 685

Gly Met Val Phe Leu Lys Gly Lys Leu Gly Val Cys Phe Asp Val Pro
 690 695 700

Thr Ala Ser Val Thr Glu Ile Gln Glu Lys Trp His Asp Ser Arg Arg
 705 710 715 720

Trp Gln Leu Ser Val Ala Thr Glu Gln Pro Glu Leu Glu Gly Pro Arg
 725 730 735

Glu Gly Tyr Gly Gly Phe Arg Gly Gln Arg Glu Gly Ser Arg Gly Phe
 740 745 750

Arg Gly Gln Arg Asp Gly Asn Arg Arg Phe Arg Gly Gln Arg Glu Gly
 755 760 765

Ser Arg Gly Pro Arg Gly Gln Arg Ser Gly Gly Gly Asn Lys Ser Asn
 770 775 780

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Arg Ser Gln Asn Lys Gly Gln Lys Arg Ser Phe Ser Lys Ala Phe Gly
 785 790 795 800

Gln

<210> 131

<211> 177

<212> PRT

<213> Homo sapiens

<400> 131

Asp Ile Phe Gln Lys Tyr Ser Asp Val Ile Ala Gly Gln Phe Tyr Gly
 1 5 10 15

His Thr His Arg Asp Ser Ile Met Val Leu Ser Asp Lys Lys Gly Ser
 20 25 30

Pro Val Asn Ser Leu Phe Val Ala Pro Ala Val Thr Pro Val Lys Ser
 35 40 45

Val Leu Glu Lys Gln Thr Asn Asn Pro Gly Ile Arg Leu Phe Gln Tyr
 50 55 60

Asp Pro Arg Asp Tyr Lys Leu Leu Asp Met Leu Gln Tyr Tyr Leu Asn
 65 70 75 80

Leu Thr Glu Ala Asn Leu Lys Gly Glu Ser Ile Trp Lys Leu Glu Tyr
 85 90 95

Ile Leu Thr Gln Thr Tyr Asp Ile Glu Asp Leu Gln Pro Glu Ser Leu
 100 105 110

Tyr Gly Leu Ala Lys Gln Phe Thr Ile Leu Asp Ser Lys Gln Phe Ile
 115 120 125

Lys Tyr Tyr Asn Tyr Phe Phe Val Ser Tyr Asp Ser Ser Val Thr Cys
 130 135 140

Asp Lys Thr Cys Lys Ala Phe Gln Ile Cys Ala Ile Met Asn Leu Asp

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145 150 155 160

Asn Ile Ser Tyr Ala Asp Cys Leu Lys Gln Leu Tyr Ile Lys His Lys
165 170 175

Tyr

<210> 132

<211> 751

<212> PRT

<213> Homo sapiens

<400> 132

Met Ala Phe Arg Thr Ile Cys Val Leu Val Gly Val Phe Ile Cys Ser
1 5 10 15

Ile Cys Val Lys Gly Ser Ser Gln Pro Gln Ala Arg Val Tyr Leu Thr
20 25 30

Phe Asp Glu Leu Arg Glu Thr Lys Thr Ser Glu Tyr Phe Ser Leu Ser
35 40 45

His His Pro Leu Asp Tyr Arg Ile Leu Leu Met Asp Glu Asp Gln Asp
50 55 60

Arg Ile Tyr Val Gly Ser Lys Asp His Ile Leu Ser Leu Asn Ile Asn
65 70 75 80

Asn Ile Ser Gln Glu Ala Leu Ser Val Phe Trp Pro Ala Ser Thr Ile
85 90 95

Lys Val Glu Glu Cys Lys Met Ala Gly Lys Asp Pro Thr His Gly Cys
100 105 110

Gly Asn Phe Val Arg Val Ile Gln Thr Phe Asn Arg Thr His Leu Tyr
115 120 125

Val	Cys	Gly	Ser	Gly	Ala	Phe	Ser	Pro	Val	Cys	Thr	Tyr	Leu	Asn	Arg
	130					135					140				

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Gly Arg Arg Ser Glu Asp Gln Val Phe Met Ile Asp Ser Lys Cys Glu
145 150 155 160

Ser Gly Lys Gly Arg Cys Ser Phe Asn Pro Asn Val Asn Thr Val Ser
165 170 175

Val Met Ile Asn Glu Glu Leu Phe Ser Gly Met Tyr Ile Asp Phe Met
180 185 190

Gly Thr Asp Ala Ala Ile Phe Arg Ser Leu Thr Lys Arg Asn Ala Val
195 200 205

Arg Thr Asp Gln His Asn Ser Lys Trp Leu Ser Glu Pro Met Phe Val
210 215 220

Asp Ala His Val Ile Pro Asp Gly Thr Asp Pro Asn Asp Ala Lys Val
225 230 235 240

Tyr Phe Phe Phe Lys Glu Lys Leu Thr Asp Asn Asn Arg Ser Thr Lys
245 250 255

Gln Ile His Ser Met Ile Ala Arg Ile Cys Pro Asn Asp Thr Gly Gly
260 265 270

Leu Arg Ser Leu Val Asn Lys Trp Thr Thr Phe Leu Lys Ala Arg Leu
275 280 285

Val Cys Ser Val Thr Asp Glu Asp Gly Pro Glu Thr His Phe Asp Glu
290 295 300

Leu Glu Asp Val Phe Leu Leu Glu Thr Asp Asn Pro Arg Thr Thr Leu
305 310 315 320

Val Tyr Gly Ile Phe Thr Thr Ser Ser Val Phe Lys Gly Ser Ala
325 330 335

Val Cys Val Tyr His Leu Ser Asp Ile Gln Thr Val Phe Asn Gly Pro
340 345 350

Phe Ala His Lys Glu Gly Pro Asn His Gln Leu Ile Ser Tyr Gln Gly
355 360 365

Arg Ile Pro Tyr Pro Arg Pro Gly Thr Cys Pro Gly Gly Ala Phe Thr
370 375 380

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Pro Asn Met Arg Thr Thr Lys Glu Phe Pro Asp Asp Val Val Thr Phe
 385 390 395 400

Ile Arg Asn His Pro Leu Met Tyr Asn Ser Ile Tyr Pro Ile His Lys
 405 410 415

Arg Pro Leu Ile Val Arg Ile Gly Thr Asp Tyr Lys Tyr Thr Lys Ile
 420 425 430

Ala Val Asp Arg Val Asn Ala Ala Asp Gly Arg Tyr His Val Leu Phe
 435 440 445

Leu Gly Thr Asp Arg Gly Thr Val Gln Lys Val Val Val Leu Pro Thr
 450 455 460

Asn Asn Ser Val Ser Gly Glu Leu Ile Leu Glu Glu Leu Glu Val Phe
 465 470 475 480

Lys Asn His Ala Pro Ile Thr Thr Met Lys Ile Ser Ser Lys Lys Gln
 485 490 495

Gln Leu Tyr Val Ser Ser Asn Glu Gly Val Ser Gln Val Ser Leu His
 500 505 510

Arg Cys His Ile Tyr Gly Thr Ala Cys Ala Asp Cys Cys Leu Ala Arg
 515 520 525

Asp Pro Tyr Cys Ala Trp Asp Gly His Ser Cys Ser Arg Phe Tyr Pro
 530 535 540

Thr Gly Lys Arg Arg Ser Arg Arg Gln Asp Val Arg His Gly Asn Pro
 545 550 555 560

Leu Thr Gln Cys Arg Gly Phe Asn Leu Lys Ala Tyr Arg Asn Ala Ala
 565 570 575

Glu Ile Val Gln Tyr Gly Val Lys Asn Asn Thr Thr Phe Leu Glu Cys
 580 585 590

Ala Pro Lys Ser Pro Gln Ala Ser Ile Lys Trp Leu Leu Gln Lys Asp
 595 600 605

Lys Asp Arg Arg Lys Glu Val Lys Leu Asn Glu Arg Ile Ile Ala Thr
 610 615 620

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Ser Gln Gly Leu Leu Ile Arg Ser Val Gln Gly Ser Asp Gln Gly Leu
625 630 635 640

Tyr His Cys Ile Ala Thr Glu Asn Ser Phe Lys Gln Thr Ile Ala Lys
645 650 655

Ile Asn Phe Lys Val Leu Asp Ser Glu Met Val Ala Val Val Thr Asp
660 665 670

Lys Trp Ser Pro Trp Thr Trp Ala Ser Ser Val Arg Ala Leu Pro Phe
675 680 685

His Pro Lys Asp Ile Met Gly Ala Phe Ser His Ser Glu Met Gln Met
690 695 700

Ile Asn Gln Tyr Cys Lys Asp Thr Arg Gln Gln His Gln Gln Gly Asp
705 710 715 720

Glu Ser Gln Lys Met Arg Gly Asp Tyr Gly Lys Leu Lys Ala Leu Ile
725 730 735

Asn Ser Arg Lys Ser Arg Asn Arg Arg Asn Gln Leu Pro Glu Ser
740 745 750

<210> 133

<211> 503

<212> PRT

<213> Homo sapiens

<400> 133

Met Glu Pro Ala Gly Pro Ala Pro Gly Arg Leu Gly Pro Leu Leu Cys
1 5 10 15

Leu Leu Leu Ala Ala Ser Cys Ala Trp Ser Gly Val Ala Gly Glu Glu
20 25 30

Glu Leu Gln Val Ile Gln Pro Asp Lys Ser Val Ser Val Ala Ala Gly
35 40 45

Glu Ser Ala Ile Leu His Cys Thr Val Thr Ser Leu Ile Pro Val Gly

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50		55		60
Pro Ile Gln Trp Phe Arg Gly Ala Gly Pro Ala Arg Glu Leu Ile Tyr				
65		70	75	80
Asn Gln Lys Glu Gly His Phe Pro Arg Val Thr Thr Val Ser Glu Ser				
	85	90		95
Thr Lys Arg Glu Asn Met Asp Phe Ser Ile Ser Ile Ser Asn Ile Thr				
	100	105		110
Pro Ala Asp Ala Gly Thr Tyr Tyr Cys Val Lys Phe Arg Lys Gly Ser				
	115	120	125	
Pro Asp Thr Glu Phe Lys Ser Gly Ala Gly Thr Glu Leu Ser Val Arg				
	130	135	140	
Ala Lys Pro Ser Ala Pro Val Val Ser Gly Pro Ala Ala Arg Ala Thr				
145		150	155	160
Pro Gln His Thr Val Ser Phe Thr Cys Glu Ser His Gly Phe Ser Pro				
	165	170		175
Arg Asp Ile Thr Leu Lys Trp Phe Lys Asn Gly Asn Glu Leu Ser Asp				
	180	185		190
Phe Gln Thr Asn Val Asp Pro Val Gly Glu Ser Val Ser Tyr Ser Ile				
	195	200	205	
His Ser Thr Ala Lys Val Val Leu Thr Arg Glu Asp Val His Ser Gln				
	210	215	220	
Val Ile Cys Glu Val Ala His Val Thr Leu Gln Gly Asp Pro Leu Arg				
225		230	235	240
Gly Thr Ala Asn Leu Ser Glu Thr Ile Arg Val Pro Pro Thr Leu Glu				
	245	250		255
Val Thr Gln Gln Pro Val Arg Ala Glu Asn Gln Val Asn Val Thr Cys				
	260	265	270	
Gln Val Arg Lys Phe Tyr Pro Gln Arg Leu Gln Leu Thr Trp Leu Glu				
	275	280	285	

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Asn Gly Asn Val Ser Arg Thr Glu Thr Ala Ser Thr Val Thr Glu Asn
 290 295 300

Lys Asp Gly Thr Tyr Asn Trp Met Ser Trp Leu Leu Val Asn Val Ser
 305 310 315 320

Ala His Arg Asp Asp Val Lys Leu Thr Cys Gln Val Glu His Asp Gly
 325 330 335

Gln Pro Ala Val Ser Lys Ser His Asp Leu Lys Val Ser Ala His Pro
 340 345 350

Lys Glu Gln Gly Ser Asn Thr Ala Ala Glu Asn Thr Gly Ser Asn Glu
 355 360 365

Arg Asn Ile Tyr Ile Val Val Gly Val Val Cys Thr Leu Leu Val Ala
 370 375 380

Leu Leu Met Ala Ala Leu Tyr Leu Val Arg Ile Arg Gln Lys Lys Ala
 385 390 395 400

Gln Gly Ser Thr Ser Ser Thr Arg Leu His Glu Pro Glu Lys Asn Ala
 405 410 415

Arg Glu Ile Thr Gln Asp Thr Asn Asp Ile Thr Tyr Ala Asp Leu Asn
 420 425 430

Leu Pro Lys Gly Lys Lys Pro Ala Pro Gln Ala Ala Glu Pro Asn Asn
 435 440 445

His Thr Glu Tyr Ala Ser Ile Gln Thr Ser Pro Gln Pro Ala Ser Glu
 450 455 460

Asp Thr Leu Thr Tyr Ala Asp Leu Asp Met Val His Leu Asn Arg Thr
 465 470 475 480

Pro Lys Gln Pro Ala Pro Lys Pro Glu Pro Ser Phe Ser Glu Tyr Ala
 485 490 495

Ser Val Gln Val Pro Arg Lys
 500

<210> 134

- 284 -

<211> 347

<212> PRT

<213> Homo sapiens

<400> 134

Met Ala Leu Leu Phe Ser Leu Ile Leu Ala Ile Cys Thr Arg Pro Gly
 1 5 10 15

Phe Leu Ala Ser Pro Ser Gly Val Arg Leu Val Gly Gly Leu His Arg
 20 25 30

Cys Glu Gly Arg Val Glu Val Glu Gln Lys Gly Gln Trp Gly Thr Val
 35 40 45

Cys Asp Asp Gly Trp Asp Ile Lys Asp Val Ala Val Leu Cys Arg Glu
 50 55 60

Leu Gly Cys Gly Ala Ala Ser Gly Thr Pro Ser Gly Ile Leu Tyr Glu
 65 70 75 80

Pro Pro Ala Glu Lys Glu Gln Lys Val Leu Ile Gln Ser Val Ser Cys
 85 90 95

Thr Gly Thr Glu Asp Thr Leu Ala Gln Cys Glu Gln Glu Glu Val Tyr
 100 105 110

Asp Cys Ser His Asp Glu Asp Ala Gly Ala Ser Cys Glu Asn Pro Glu
 115 120 125

Ser Ser Phe Ser Pro Val Pro Glu Gly Val Arg Leu Ala Asp Gly Pro
 130 135 140

Gly His Cys Lys Gly Arg Val Glu Val Lys His Gln Asn Gln Trp Tyr
 145 150 155 160

Thr Val Cys Gln Thr Gly Trp Ser Leu Arg Ala Ala Lys Val Val Cys
 165 170 175

Arg Gln Leu Gly Cys Gly Arg Ala Val Leu Thr Gln Lys Arg Cys Asn
 180 185 190

Lys His Ala Tyr Gly Arg Lys Pro Ile Trp Leu Ser Gln Met Ser Cys

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195	200	205
Ser Gly Arg Glu Ala Thr Leu Gln Asp Cys Pro Ser Gly Pro Trp Gly		
210	215	220
Lys Asn Thr Cys Asn His Asp Glu Asp Thr Trp Val Glu Cys Glu Asp		
225	230	235
Pro Phe Asp Leu Arg Leu Val Gly Gly Asp Asn Leu Cys Ser Gly Arg		
	245	250
Leu Glu Val Leu His Lys Gly Val Trp Gly Ser Val Cys Asp Asp Asn		
	260	265
Trp Gly Glu Lys Glu Asp Gln Val Val Cys Lys Gln Leu Gly Cys Gly		
	275	280
Lys Ser Leu Ser Pro Ser Phe Arg Asp Arg Lys Cys Tyr Gly Pro Gly		
	290	295
Val Gly Arg Ile Trp Leu Asp Asn Val Arg Cys Ser Gly Glu Glu Gln		
305	310	315
Ser Leu Glu Gln Cys Gln His Arg Phe Trp Gly Phe His Asp Cys Thr		
	325	330
His Gln Glu Asp Val Ala Val Ile Cys Ser Gly		
	340	345
<210> 135		
<211> 277		
<212> PRT		
<213> Homo sapiens		
<400> 135		
Met Ala Ala Val Ser Val Tyr Ala Pro Pro Val Gly Gly Phe Ser Phe		
1	5	10
Asp Asn Cys Arg Arg Asn Ala Val Leu Glu Ala Asp Phe Ala Lys Arg		
20	25	30

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Gly Tyr Lys Leu Pro Lys Val Arg Lys Thr Gly Thr Thr Ile Ala Gly
35 40 45

Val Val Tyr Lys Asp Gly Ile Val Leu Gly Ala Asp Thr Arg Ala Thr
50 55 60

Glu Gly Met Val Val Ala Asp Lys Asn Cys Ser Lys Ile His Phe Ile
65 70 75 80

Ser Pro Asn Ile Tyr Cys Cys Gly Ala Gly Thr Ala Ala Asp Thr Asp
85 90 95

Met Thr Thr Gln Leu Ile Ser Ser Asn Leu Glu Leu His Ser Leu Ser
100 105 110

Thr Gly Arg Leu Pro Arg Val Val Thr Ala Asn Arg Met Leu Lys Gln
115 120 125

Met Leu Phe Arg Tyr Gln Gly Tyr Ile Gly Ala Ala Leu Val Leu Gly
130 135 140

Gly Val Asp Val Thr Gly Pro His Leu Tyr Ser Ile Tyr Pro His Gly
145 150 155 160

Ser Thr Asp Lys Leu Pro Tyr Val Thr Met Gly Ser Gly Ser Leu Ala
165 170 175

Ala Met Ala Val Phe Glu Asp Lys Phe Arg Pro Asp Met Glu Glu Glu
180 185 190

Glu Ala Lys Asn Leu Val Ser Glu Ala Ile Ala Ala Gly Ile Phe Asn
195 200 205

Asp Leu Gly Ser Gly Ser Asn Ile Asp Leu Cys Val Ile Ser Lys Asn
210 215 220

Lys Leu Asp Phe Leu Arg Pro Tyr Thr Val Pro Asn Lys Lys Gly Thr
225 230 235 240

Arg Leu Gly Arg Tyr Arg Cys Glu Lys Gly Thr Thr Ala Val Leu Thr
245 250 255

Glu Lys Ile Thr Pro Leu Glu Ile Glu Val Leu Glu Glu Thr Val Gln
260 265 270

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Thr Met Asp Thr Ser
275

<210> 136

<211> 763

<212> PRT

<213> Homo sapiens

<400> 136

Met Ala Ala Thr Gly Thr Ala Ala Ala Ala Ala Thr Gly Arg Leu Leu
1 5 10 15

Leu Leu Leu Leu Val Gly Leu Thr Ala Pro Ala Leu Ala Leu Ala Gly
20 25 30

Tyr Ile Glu Ala Leu Ala Ala Asn Ala Gly Thr Gly Phe Ala Val Ala
35 40 45

Glu Pro Gln Ile Ala Met Phe Cys Gly Lys Leu Asn Met His Val Asn
50 55 60

Ile Gln Thr Gly Lys Trp Glu Pro Asp Pro Thr Gly Thr Lys Ser Cys
65 70 75 80

Phe Glu Thr Lys Glu Glu Val Leu Gln Tyr Cys Gln Glu Met Tyr Pro
85 90 95

Glu Leu Gln Ile Thr Asn Val Met Glu Ala Asn Gln Arg Val Ser Ile
100 105 110

Asp Asn Trp Cys Arg Arg Asp Lys Lys Gln Cys Lys Ser Arg Phe Val
115 120 125

Thr Pro Phe Lys Cys Leu Val Gly Glu Phe Val Ser Asp Val Leu Leu
130 135 140

Val Pro Glu Lys Cys Gln Phe Phe His Lys Glu Arg Met Glu Val Cys
145 150 155 160

Glu Asn His Gln His Trp His Thr Val Val Lys Glu Ala Cys Leu Thr
165 170 175

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Gln Gly Met Thr Leu Tyr Ser Tyr Gly Met Leu Leu Pro Cys Gly Val
 180 185 190

Asp Gln Phe His Gly Thr Glu Tyr Val Cys Cys Pro Gln Thr Lys Ile
 195 200 205

Ile Gly Ser Val Ser Lys Glu Glu Glu Glu Asp Glu Glu Glu Glu
 210 215 220

Glu Glu Glu Asp Glu Glu Glu Asp Tyr Asp Val Tyr Lys Ser Glu Phe
 225 230 235 240

Pro Thr Glu Ala Asp Leu Glu Asp Phe Thr Glu Ala Ala Val Asp Glu
 245 250 255

Asp Asp Glu Asp Glu Glu Glu Gly Glu Glu Val Val Glu Asp Arg Asp
 260 265 270

Tyr Tyr Tyr Asp Thr Phe Lys Gly Asp Asp Tyr Asn Glu Glu Asn Pro
 275 280 285

Thr Glu Pro Gly Ser Asp Gly Thr Met Ser Asp Lys Glu Ile Thr His
 290 295 300

Asp Val Lys Ala Val Cys Ser Gln Glu Ala Met Thr Gly Pro Cys Arg
 305 310 315 320

Ala Val Met Pro Arg Trp Tyr Phe Asp Leu Ser Lys Gly Lys Cys Val
 325 330 335

Arg Phe Ile Tyr Gly Gly Cys Gly Gly Asn Arg Asn Asn Phe Glu Ser
 340 345 350

Glu Asp Tyr Cys Met Ala Val Cys Lys Ala Met Ile Pro Pro Thr Pro
 355 360 365

Leu Pro Thr Asn Asp Val Asp Val Tyr Phe Glu Thr Ser Ala Asp Asp
 370 375 380

Asn Glu His Ala Arg Phe Gln Lys Ala Lys Glu Gln Leu Glu Ile Arg
 385 390 395 400

His Arg Asn Arg Met Asp Arg Val Lys Lys Glu Trp Glu Glu Ala Glu

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405	410	415
Leu Gln Ala Lys Asn Leu Pro Lys Ala Glu Arg Gln Thr Leu Ile Gln 420 425 430		
His Phe Gln Ala Met Val Lys Ala Leu Glu Lys Glu Ala Ala Ser Glu 435 440 445		
Lys Gln Gln Leu Val Glu Thr His Leu Ala Arg Val Glu Ala Met Leu 450 455 460		
Asn Asp Arg Arg Arg Met Ala Leu Glu Asn Tyr Leu Ala Ala Leu Gln 465 470 475 480		
Ser Asp Pro Pro Arg Pro His Arg Ile Leu Gln Ala Leu Arg Arg Tyr 485 490 495		
Val Arg Ala Glu Asn Lys Asp Arg Leu His Thr Ile Arg His Tyr Gln 500 505 510		
His Val Leu Ala Val Asp Pro Glu Lys Ala Ala Gln Met Lys Ser Gln 515 520 525		
Val Met Thr His Leu His Val Ile Glu Glu Arg Arg Asn Gln Ser Leu 530 535 540		
Ser Leu Leu Tyr Lys Val Pro Tyr Val Ala Gln Glu Ile Gln Glu Glu 545 550 555 560		
Ile Asp Glu Leu Leu Gln Glu Gln Arg Ala Asp Met Asp Gln Phe Thr 565 570 575		
Ala Ser Ile Ser Glu Thr Pro Val Asp Val Arg Val Ser Ser Glu Glu 580 585 590		
Ser Glu Glu Ile Pro Pro Phe His Pro Phe His Pro Phe Pro Ala Leu 595 600 605		
Pro Glu Asn Glu Asp Thr Gln Pro Glu Leu Tyr His Pro Met Lys Lys 610 615 620		
Gly Ser Gly Val Gly Glu Gln Asp Gly Gly Leu Ile Gly Ala Glu Glu 625 630 635 640		

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Lys Val Ile Asn Ser Lys Asn Lys Val Asp Glu Asn Met Val Ile Asp
 645 650 655

Glu Thr Leu Asp Val Lys Glu Met Ile Phe Asn Ala Glu Arg Val Gly
 660 665 670

Gly Leu Glu Glu Glu Arg Glu Ser Val Gly Pro Leu Arg Glu Asp Phe
 675 680 685

Ser Leu Ser Ser Ser Ala Leu Ile Gly Leu Leu Val Ile Ala Val Ala
 690 695 700

Ile Ala Thr Val Ile Val Ile Ser Leu Val Met Leu Arg Lys Arg Gln
 705 710 715 720

Tyr Gly Thr Ile Ser His Gly Ile Val Glu Val Asp Pro Met Leu Thr
 725 730 735

Pro Glu Glu Arg His Leu Asn Lys Met Gln Asn His Gly Tyr Glu Asn
 740 745 750

Pro Thr Tyr Lys Tyr Leu Glu Gln Met Gln Ile
 755 760

<210> 137

<211> 251

<212> PRT

<213> Homo sapiens

<400> 137

Met Lys Ile Ser Phe Ile Glu Pro Ala Ile Leu Leu Asn Ala Phe Ala
 1 5 10 15

Met Thr Leu Thr Ile Pro Leu Thr Ala Gln Tyr Val Tyr Arg Arg Ile
 20 25 30

Trp Glu Glu Thr Gly Asn Tyr Thr Phe Ala Ser Asn Gly Ser Glu Cys
 35 40 45

Asp Gln Asn Lys Ser Ser Ser Ile Phe Ala Phe Arg Glu Glu Val Gln
 50 55 60

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Lys Lys Ala Ser Leu Phe Asn Leu Gln Val Glu Met Ser Ala Leu Ile
 65 70 75 80

Pro Gly Leu Val Ser Thr Phe Met Leu Leu Ala Ser Ser Asp Asn His
 85 90 95

Gly Arg Lys Leu Pro Met Val Leu Ser Ser Leu Gly Ser Leu Gly Thr
 100 105 110

Asn Thr Trp Leu Cys Met Met Ser Tyr Phe Asp Leu Pro Leu Gln Leu
 115 120 125

Leu Ile Ala Ser Thr Phe Ile Gly Ala Leu Phe Gly Asn Tyr Thr Thr
 130 135 140

Phe Trp Gly Ala Cys Phe Ala Tyr Ile Val Asp Gln Gln Lys Glu Tyr
 145 150 155 160

Lys His Arg Ile Ile Arg Ile Ala Ile Leu Asp Phe Met Leu Gly Val
 165 170 175

Val Thr Gly Leu Thr Gly Leu Ser Ser Gly Tyr Phe Ile Arg Glu Leu
 180 185 190

Gly Phe Val Trp Ser Tyr Phe Ile Thr Ala Met Val Leu Ile Val Asn
 195 200 205

Leu Ala Tyr Ile Leu Phe Phe Leu Asn Asp Pro Ile Lys Glu Ser Ser
 210 215 220

Ser Gln Ile Val Thr Met Ser Cys Ile Glu Ser Leu Lys Asp Leu Phe
 225 230 235 240

Tyr Arg Thr Tyr Met Leu Phe Lys Asn Gly Ser
 245 250

<210> 138

<211> 283

<212> PRT

<213> Homo sapiens

- 292 -

<400> 138

Met Ala Val Pro Pro Thr Tyr Ala Asp Leu Gly Lys Ser Ala Arg Asp
 1 5 10 15

Val Phe Thr Lys Gly Tyr Gly Phe Gly Leu Ile Lys Leu Asp Leu Lys
 20 25 30

Thr Lys Ser Glu Asn Gly Leu Glu Phe Thr Ser Ser Gly Ser Ala Asn
 35 40 45

Thr Glu Thr Thr Lys Val Thr Gly Ser Leu Glu Thr Lys Tyr Arg Trp
 50 55 60

Thr Glu Tyr Gly Leu Thr Phe Thr Glu Lys Trp Asn Thr Asp Asn Thr
 65 70 75 80

Leu Gly Thr Glu Ile Thr Val Glu Asp Gln Leu Ala Arg Gly Leu Lys
 85 90 95

Leu Thr Phe Asp Ser Ser Phe Ser Pro Asn Thr Gly Lys Lys Asn Ala
 100 105 110

Lys Ile Lys Thr Gly Tyr Lys Arg Glu His Ile Asn Leu Gly Cys Asp
 115 120 125

Met Asp Phe Asp Ile Ala Gly Pro Ser Ile Arg Gly Ala Leu Val Leu
 130 135 140

Gly Tyr Glu Gly Trp Leu Ala Gly Tyr Gln Met Asn Phe Glu Thr Ala
 145 150 155 160

Lys Ser Arg Val Thr Gln Ser Asn Phe Ala Val Gly Tyr Lys Thr Asp
 165 170 175

Glu Phe Gln Leu His Thr Asn Val Asn Asp Gly Thr Glu Phe Gly Gly
 180 185 190

Ser Ile Tyr Gln Lys Val Asn Lys Lys Leu Glu Thr Ala Val Asn Leu
 195 200 205

Ala Trp Thr Ala Gly Asn Ser Asn Thr Arg Phe Gly Ile Ala Ala Lys
 210 215 220

Tyr Gln Ile Asp Pro Asp Ala Cys Phe Ser Ala Lys Val Asn Asn Ser

225 230 235 240

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Tyr Leu Gly Gln Phe Pro Asp Ile Lys Ser Arg Ile Ala Lys Arg Gly
 130 135 140

Arg Lys Leu Val Asp Tyr Asp Ser Ala Arg His His Tyr Glu Ser Leu
 145 150 155 160

Gln Thr Ala Lys Lys Lys Asp Glu Ala Lys Ile Ala Lys Ala Glu Glu
 165 170 175

Glu Leu Ile Lys Ala Gln Lys Val Phe Glu Glu Met Asn Val Asp Leu
 180 185 190

Gln Glu Glu Leu Pro Ser Leu Trp Asn Ser Arg Val Gly Phe Tyr Val
 195 200 205

Asn Thr Phe Gln Ser Ile Ala Gly Leu Glu Glu Asn Phe His Lys Glu
 210 215 220

Met Ser Lys Leu Asn Gln Asn Leu Asn Asp Val Leu Val Gly Leu Glu
 225 230 235 240

Lys Gln His Gly Ser Asn Thr Phe Thr Val Lys Ala Gln Pro Ser Asp
 245 250 255

Asn Ala Pro Ala Lys Gly Asn Lys Ser Pro Ser Pro Pro Asp Gly Ser
 260 265 270

Pro Ala Ala Thr Pro Glu Ile Arg Val Asn His Glu Pro Glu Pro Ala
 275 280 285

Gly Gly Ala Thr Pro Gly Ala Thr Leu Pro Lys Ser Pro Ser Gln Leu
 290 295 300

Arg Lys Gly Pro Pro Val Pro Pro Pro Pro Lys His Thr Pro Ser Lys
 305 310 315 320

Glu Val Lys Gln Glu Gln Ile Leu Ser Leu Phe Glu Asp Thr Phe Val
 325 330 335

Pro Glu Ile Ser Val Thr Thr Pro Ser Gln Pro Ala Glu Ala Ser Glu
 340 345 350

Val Ala Gly Gly Thr Gln Pro Ala Ala Gly Ala Gln Glu Pro Gly Glu
 355 360 365

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Thr Ala Ala Ser Glu Ala Ala Ser Ser Ser Leu Pro Ala Val Val Val
 370 375 380

Glu Thr Phe Pro Ala Thr Val Asn Gly Thr Val Glu Gly Gly Ser Gly
 385 390 395 400

Ala Gly Arg Leu Asp Leu Pro Pro Gly Phe Met Phe Lys Val Gln Ala
 405 410 415

Gln His Asp Tyr Thr Ala Thr Asp Thr Asp Glu Leu Gln Leu Lys Ala
 420 425 430

Gly Asp Val Val Leu Val Ile Pro Phe Gln Asn Pro Glu Glu Gln Asp
 435 440 445

Glu Gly Trp Leu Met Gly Val Lys Glu Ser Asp Trp Asn Gln His Lys
 450 455 460

Glu Leu Glu Lys Cys Arg Gly Val Phe Pro Glu Asn Phe Thr Glu Arg
 465 470 475 480

Val Pro

<210> 140

<211> 1053

<212> PRT

<213> Homo sapiens

<400> 140

Met Ser Ser Glu Glu Ser Tyr Arg Ala Ile Leu Arg Tyr Leu Thr Asn
 1 5 10 15

Glu Arg Glu Pro Tyr Ala Pro Gly Thr Glu Gly Asn Val Lys Arg Lys
 20 25 30

Ile Arg Lys Ala Ala Ala Cys Tyr Val Val Arg Gly Gly Thr Leu Tyr
 35 40 45

Tyr Gln Arg Arg Gln Arg His Arg Lys Thr Phe Ala Glu Leu Glu Val
 50 55 60

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Val Leu Gln Pro Glu Arg Arg Arg Asp Leu Ile Glu Ala Ala His Leu
 65 70 75 80

Gly Pro Gly Gly Thr His His Thr Arg His Gln Thr Trp His Tyr Leu
 85 90 95

Ser Lys Thr Tyr Trp Trp Arg Gly Ile Leu Lys Gln Val Lys Asp Tyr
 100 105 110

Ile Lys Gln Cys Ser Lys Cys Gln Glu Lys Leu Asp Arg Ser Arg Pro
 115 120 125

Ile Ser Asp Val Ser Glu Met Leu Glu Glu Leu Gly Leu Asp Leu Glu
 130 135 140

Ser Gly Glu Glu Ser Asn Glu Ser Glu Asp Asp Leu Ser Asn Phe Thr
 145 150 155 160

Ser Ser Pro Thr Thr Ala Ser Lys Pro Ala Lys Lys Lys Pro Val Ser
 165 170 175

Lys His Glu Leu Val Phe Val Asp Thr Lys Gly Val Val Lys Arg Ser
 180 185 190

Ser Pro Lys His Cys Gln Ala Val Leu Lys Gln Leu Asn Glu Gln Arg
 195 200 205

Leu Ser Asn Gln Phe Cys Asp Val Thr Leu Leu Ile Glu Gly Glu Glu
 210 215 220

Tyr Lys Ala His Lys Ser Val Leu Ser Ala Asn Ser Glu Tyr Phe Arg
 225 230 235 240

Asp Leu Phe Ile Glu Lys Gly Ala Val Ser Ser His Glu Ala Val Val
 245 250 255

Asp Leu Ser Gly Phe Cys Lys Ala Ser Phe Leu Pro Leu Leu Glu Phe
 260 265 270

Ala Tyr Thr Ser Val Leu Ser Phe Asp Phe Cys Ser Met Ala Asp Val
 275 280 285

Ala Ile Leu Ala Arg His Leu Phe Met Ser Glu Val Leu Glu Ile Cys

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290		295		300
Glu Ser Val His Lys Leu Met Glu Glu Lys Gln Leu Thr Val Tyr Lys				
305		310		315 320
Lys Gly Glu Val Gln Thr Val Ala Ser Thr Gln Asp Leu Arg Val Gln				
	325		330	335
Asn Gly Gly Thr Ala Pro Pro Val Ala Ser Ser Glu Gly Thr Thr Thr				
	340		345	350
Ser Leu Pro Thr Glu Leu Gly Asp Cys Glu Ile Val Leu Leu Val Asn				
	355		360	365
Gly Glu Leu Pro Glu Ala Glu Gln Asn Gly Glu Val Gly Arg Gln Pro				
	370		375	380
Glu Pro Gln Val Ser Ser Glu Ala Glu Ser Ala Leu Ser Ser Val Gly				
385		390		395 400
Cys Ile Ala Asp Ser His Pro Glu Met Glu Ser Val Asp Leu Ile Thr				
	405		410	415
Lys Asn Asn Gln Thr Glu Leu Glu Thr Ser Asn Asn Arg Glu Asn Asn				
	420		425	430
Thr Val Ser Asn Ile His Pro Lys Leu Ser Lys Glu Asn Val Ile Ser				
	435		440	445
Ser Ser Pro Glu Asp Ser Gly Met Gly Asn Asp Ile Ser Ala Glu Asp				
	450		455	460
Ile Cys Ala Glu Asp Ile Pro Lys His Arg Gln Lys Val Asp Gln Pro				
465		470		475 480
Leu Lys Asp Gln Glu Asn Leu Val Ala Ser Thr Ala Lys Thr Asn Phe				
	485		490	495
Gly Pro Asp Asp Asp Thr Tyr Arg Ser Arg Leu Arg Gln Arg Ser Val				
	500		505	510
Asn Glu Gly Ala Tyr Ile Arg Leu His Lys Gly Met Glu Lys Lys Leu				
	515		520	525

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Gln Lys Arg Lys Ala Val Pro Lys Ser Ala Val Gln Gln Val Ala Gln
 530 535 540

Lys Leu Val Gln Arg Gly Lys Lys Met Lys Gln Pro Lys Arg Asp Ala
 545 550 555 560

Lys Glu Asn Thr Glu Glu Ala Ser His Lys Cys Gly Glu Cys Gly Met
 565 570 575

Val Phe Gln Arg Arg Tyr Ala Leu Ile Met His Lys Leu Lys His Glu
 580 585 590

Arg Ala Arg Asp Tyr Lys Cys Pro Leu Cys Lys Lys Gln Phe Gln Tyr
 595 600 605

Ser Ala Ser Leu Arg Ala His Leu Ile Arg His Thr Arg Lys Asp Ala
 610 615 620

Pro Ser Ser Ser Ser Ser Asn Ser Thr Ser Asn Glu Ala Ser Gly Thr
 625 630 635 640

Ser Ser Glu Lys Gly Arg Thr Lys Arg Glu Phe Ile Cys Ser Ile Cys
 645 650 655

Gly Arg Thr Leu Pro Lys Leu Tyr Ser Leu Arg Ile His Met Leu Lys
 660 665 670

His Thr Gly Val Lys Pro His Ala Cys Gln Val Cys Gly Lys Thr Phe
 675 680 685

Ile Tyr Lys His Gly Leu Lys Leu His Gln Ser Leu His Gln Ser Gln
 690 695 700

Lys Gln Phe Gln Cys Glu Leu Cys Val Lys Ser Phe Val Thr Lys Arg
 705 710 715 720

Ser Leu Gln Glu His Met Ser Ile His Thr Gly Glu Ser Lys Tyr Leu
 725 730 735

Cys Ser Val Cys Gly Lys Ser Phe His Arg Gly Ser Gly Leu Ser Lys
 740 745 750

His Phe Lys Lys His Gln Pro Lys Pro Glu Val Arg Gly Tyr His Cys
 755 760 765

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Thr Gln Cys Glu Lys Ser Phe Phe Glu Ala Arg Asp Leu Arg Gln His
 770 775 780

Met Asn Lys His Leu Gly Val Lys Pro Phe Gln Cys Gln Phe Cys Asp
 785 790 795 800

Lys Cys Tyr Ser Trp Lys Lys Asp Trp Tyr Ser His Val Lys Ser His
 805 810 815

Ser Val Thr Glu Pro Tyr Arg Cys Asn Ile Cys Gly Lys Glu Phe Tyr
 820 825 830

Glu Lys Ala Leu Phe Arg Arg His Val Lys Lys Ala Thr His Gly Lys
 835 840 845

Lys Gly Arg Ala Lys Gln Asn Leu Glu Arg Val Cys Glu Lys Cys Gly
 850 855 860

Arg Lys Phe Thr Gln Leu Arg Glu Tyr Arg Arg His Met Asn Asn His
 865 870 875 880

Glu Gly Val Lys Pro Phe Glu Cys Leu Thr Cys Gly Val Ala Trp Ala
 885 890 895

Asp Ala Arg Ser Leu Lys Arg His Val Arg Thr His Thr Gly Glu Arg
 900 905 910

Pro Tyr Val Cys Pro Val Cys Ser Glu Ala Tyr Ile Asp Ala Arg Thr
 915 920 925

Leu Arg Lys His Met Thr Lys Phe His Arg Asp Tyr Val Pro Cys Lys
 930 935 940

Ile Met Leu Glu Lys Asp Thr Leu Gln Phe His Asn Gln Gly Thr Gln
 945 950 955 960

Val Ala His Ala Val Ser Ile Leu Thr Ala Gly Met Gln Glu Gln Glu
 965 970 975

Ser Ser Gly Pro Gln Glu Leu Glu Thr Val Val Val Thr Gly Glu Thr
 980 985 990

Met Glu Ala Leu Glu Ala Val Ala Ala Thr Glu Glu Tyr Pro Ser Val
 995 1000 1005

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Ser Thr Leu Ser Asp Gln Ser Ile Met Gln Val Val Asn Tyr Val
 1010 1015 1020

Leu Ala Gln Gln Gln Gly Gln Lys Leu Ser Glu Val Ala Glu Ala
 1025 1030 1035

Ile Gln Thr Val Lys Val Glu Val Ala His Ile Ser Gly Gly Glu
 1040 1045 1050

<210> 141

<211> 143

<212> PRT

<213> Homo sapiens

<400> 141

Met Ser Gln Thr Arg Asp Leu Gln Gly Gly Lys Ala Phe Gly Leu Leu
 1 5 10 15

Lys Ala Gln Gln Glu Glu Arg Leu Asp Glu Ile Asn Lys Gln Phe Leu
 20 25 30

His Asp Pro Lys Tyr Ser Ser Asp Glu Asp Leu Pro Ser Lys Leu Glu
 35 40 45

Gly Phe Lys Glu Lys Tyr Met Glu Phe Asp Leu Asn Gly Asn Gly Asp
 50 55 60

Ile Asp Ile Met Ser Leu Lys Arg Met Leu Glu Lys Leu Gly Val Pro
 65 70 75 80

Lys Thr His Leu Glu Leu Lys Lys Leu Ile Gly Glu Val Ser Ser Gly
 85 90 95

Ser Gly Glu Thr Phe Ser Tyr Pro Asp Phe Leu Arg Met Met Leu Gly
 100 105 110

Lys Arg Ser Ala Ile Leu Lys Met Ile Leu Met Tyr Glu Glu Lys Ala
 115 120 125

Arg Glu Arg Lys Thr Asn Thr Pro Pro Ser Gln Glu Ser Pro Ile

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130 135 140

<210> 142

<211> 178

<212> PRT

<213> Homo sapiens

<400> 142

Met His Val Asn Gly Lys Val Ala Leu Val Thr Gly Ala Ala Gln Gly
1 5 10 15

Ile Gly Arg Ala Phe Ala Glu Ala Leu Leu Leu Lys Gly Ala Lys Val
 20 25 30

Ala Leu Val Asp Trp Asn Leu Glu Ala Gly Val Gln Cys Lys Ala Ala
 35 40 45

Leu Asp Glu Gln Phe Glu Pro Gln Lys Thr Leu Phe Ile Gln Cys Asp
50 55 60

Val Ala Asp Gln Gln Gln Leu Arg Asp Thr Phe Arg Lys Val Val Asp
65 70 75 80

His Phe Gly Arg Leu Asp Ile Leu Val Asn Asn Ala Gly Val Asn Asn
 85 90 95

Lys Lys Asn Trp Glu Lys Thr Leu Gln Ile Asn Leu Val Ser Val Ile
 100 105 110

Ser Gly Thr Tyr Leu Gly Leu Asp Tyr Met Ser Lys Gln Asn Gly Gly
 115 120 125

Glu Gly Gly Ile Ile Ile Asn Met Ser Ser Leu Ala Gly Leu Met Pro
130 135 140

Val Ala Gln Gln Pro Val Tyr Cys Ala Ser Lys His Gly Ile Val Gly
145 150 155 160

Phe Thr Arg Ser Ala Ala Pro Thr Ile Asp Cys Gln Trp Ile Asp Asn
 165 170 175

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Thr His

<210> 143

<211> 687

<212> PRT

<213> Homo sapiens

<400> 143

Met Ala Glu Glu Leu Val Leu Glu Arg Cys Asp Leu Glu Leu Glu Thr
 1 5 10 15

Asn Gly Arg Asp His His Thr Ala Asp Leu Cys Arg Glu Lys Leu Val
 20 25 30

Val Arg Arg Gly Gln Pro Phe Trp Leu Thr Leu His Phe Glu Gly Arg
 35 40 45

Asn Tyr Gln Ala Ser Val Asp Ser Leu Thr Phe Ser Val Val Thr Gly
 50 55 60

Pro Ala Pro Ser Gln Glu Ala Gly Thr Lys Ala Arg Phe Pro Leu Arg
 65 70 75 80

Asp Ala Val Glu Glu Gly Asp Trp Thr Ala Thr Val Val Asp Gln Gln
 85 90 95

Asp Cys Thr Leu Ser Leu Gln Leu Thr Thr Pro Ala Asn Ala Pro Ile
 100 105 110

Gly Leu Tyr Arg Leu Ser Leu Glu Ala Ser Thr Gly Tyr Gln Gly Ser
 115 120 125

Ser Phe Val Leu Gly His Phe Ile Leu Leu Phe Asn Ala Trp Cys Pro
 130 135 140

Ala Asp Ala Val Tyr Leu Asp Ser Glu Glu Glu Arg Gln Glu Tyr Val
 145 150 155 160

Leu Thr Gln Gln Gly Phe Ile Tyr Gln Gly Ser Ala Lys Phe Ile Lys
 165 170 175

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Asn Ile Pro Trp Asn Phe Gly Gln Phe Gln Asp Gly Ile Leu Asp Ile
 180 185 190

Cys Leu Ile Leu Leu Asp Val Asn Pro Lys Phe Leu Lys Asn Ala Gly
 195 200 205

Arg Asp Cys Ser Arg Arg Ser Ser Pro Val Tyr Val Gly Arg Val Gly
 210 215 220

Ser Gly Met Val Asn Cys Asn Asp Asp Gln Gly Val Leu Leu Gly Arg
 225 230 235 240

Trp Asp Asn Asn Tyr Gly Asp Gly Val Ser Pro Met Ser Trp Ile Gly
 245 250 255

Ser Val Asp Ile Leu Arg Arg Trp Lys Asn His Gly Cys Gln Arg Val
 260 265 270

Lys Tyr Gly Gln Cys Trp Val Phe Ala Ala Val Ala Cys Thr Val Leu
 275 280 285

Arg Cys Leu Gly Ile Pro Thr Arg Val Val Thr Asn Tyr Asn Ser Ala
 290 295 300

His Asp Gln Asn Ser Asn Leu Leu Ile Glu Tyr Phe Arg Asn Glu Phe
 305 310 315 320

Gly Glu Ile Gln Gly Asp Lys Ser Glu Met Ile Trp Asn Phe His Cys
 325 330 335

Trp Val Glu Ser Trp Met Thr Arg Pro Asp Leu Gln Pro Gly Tyr Glu
 340 345 350

Gly Trp Gln Ala Leu Asp Pro Thr Pro Gln Glu Lys Ser Glu Gly Thr
 355 360 365

Tyr Cys Cys Gly Pro Val Pro Val Arg Ala Ile Lys Glu Gly Asp Leu
 370 375 380

Ser Thr Lys Tyr Asp Ala Pro Phe Val Phe Ala Glu Val Asn Ala Asp
 385 390 395 400

Val Val Asp Trp Ile Gln Gln Asp Asp Gly Ser Val His Lys Ser Ile
 405 410 415

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Asn Arg Ser Leu Ile Val Gly Leu Lys Ile Ser Thr Lys Ser Val Gly
 420 425 430

Arg Asp Glu Arg Glu Asp Ile Thr His Thr Tyr Lys Tyr Pro Glu Gly
 435 440 445

Ser Ser Glu Glu Arg Glu Ala Phe Thr Arg Ala Asn His Leu Asn Lys
 450 455 460

Leu Ala Glu Lys Glu Glu Thr Gly Met Ala Met Arg Ile Arg Val Gly
 465 470 475 480

Gln Ser Met Asn Met Gly Ser Asp Phe Asp Val Phe Ala His Ile Thr
 485 490 495

Asn Asn Thr Ala Glu Glu Tyr Val Cys Arg Leu Leu Leu Cys Ala Arg
 500 505 510

Thr Val Ser Tyr Asn Gly Ile Leu Gly Pro Glu Cys Gly Thr Lys Tyr
 515 520 525

Leu Leu Asn Leu Thr Leu Glu Pro Phe Ser Glu Lys Ser Val Pro Leu
 530 535 540

Cys Ile Leu Tyr Glu Lys Tyr Arg Asp Cys Leu Thr Glu Ser Asn Leu
 545 550 555 560

Ile Lys Val Arg Ala Leu Leu Val Glu Pro Val Ile Asn Ser Tyr Leu
 565 570 575

Leu Ala Glu Arg Asp Leu Tyr Leu Glu Asn Pro Glu Ile Lys Ile Arg
 580 585 590

Ile Leu Gly Glu Pro Lys Gln Lys Arg Lys Leu Val Ala Glu Val Ser
 595 600 605

Leu Gln Asn Pro Leu Pro Val Ala Leu Glu Gly Cys Thr Phe Thr Val
 610 615 620

Glu Gly Ala Gly Leu Thr Glu Glu Gln Lys Thr Val Glu Ile Pro Asp
 625 630 635 640

Pro Val Glu Ala Gly Glu Glu Val Lys Val Arg Met Asp Leu Val Pro

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645

650

655

Leu His Met Gly Leu His Lys Leu Val Val Asn Phe Glu Ser Asp Lys
 660 665 670

Leu Lys Ala Val Lys Gly Phe Arg Asn Val Ile Ile Gly Pro Ala
 675 680 685

<210> 144

<211> 277

<212> PRT

<213> Homo sapiens

<400> 144

Met Ala Ala Val Ser Val Tyr Ala Pro Pro Val Gly Gly Phe Ser Phe
 1 5 10 15

Asp Asn Cys Arg Arg Asn Ala Val Leu Glu Ala Asp Phe Ala Lys Arg
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Gly Tyr Lys Leu Pro Lys Val Arg Lys Thr Gly Thr Thr Ile Ala Gly
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Val Val Tyr Lys Asp Gly Ile Val Leu Gly Ala Asp Thr Arg Ala Thr
 50 55 60

Glu Gly Met Val Val Ala Asp Lys Asn Cys Ser Lys Ile His Phe Ile
 65 70 75 80

Ser Pro Asn Ile Tyr Cys Cys Gly Ala Gly Thr Ala Ala Asp Thr Asp
 85 90 95

Met Thr Thr Gln Leu Ile Ser Ser Asn Leu Glu Leu His Ser Leu Ser
 100 105 110

Thr Gly Arg Leu Pro Arg Val Val Thr Ala Asn Arg Met Leu Lys Gln
 115 120 125

Met Leu Phe Arg Tyr Gln Gly Tyr Ile Gly Ala Ala Leu Val Leu Gly
 130 135 140

- 306 -

Gly Val Asp Val Thr Gly Pro His Leu Tyr Ser Ile Tyr Pro His Gly
 145 150 155 160

Ser Thr Asp Lys Leu Pro Tyr Val Thr Met Gly Ser Gly Ser Leu Ala
 165 170 175

Ala Met Ala Val Phe Glu Asp Lys Phe Arg Pro Asp Met Glu Glu Glu
 180 185 190

Glu Ala Lys Asn Leu Val Ser Glu Ala Ile Ala Ala Gly Ile Phe Asn
 195 200 205

Asp Leu Gly Ser Gly Ser Asn Ile Asp Leu Cys Val Ile Ser Lys Asn
 210 215 220

Lys Leu Asp Phe Leu Arg Pro Tyr Thr Val Pro Asn Lys Lys Gly Thr
 225 230 235 240

Arg Leu Gly Arg Tyr Arg Cys Glu Lys Gly Thr Thr Ala Val Leu Thr
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Thr Met Asp Thr Ser
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<210> 145

<211> 972

<212> PRT

<213> Homo sapeins

<400> 145

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Gly Gln Gly Ile Pro Val Ile Glu Pro Ser Val Pro Glu Leu Val Val
 20 25 30

Lys Pro Gly Ala Thr Val Thr Leu Arg Cys Val Gly Asn Gly Ser Val
 35 40 45

- 307 -

Glu Trp Asp Gly Pro Ala Ser Pro His Trp Thr Leu Tyr Ser Asp Gly
 50 55 60

Ser Ser Ser Ile Leu Ser Thr Asn Asn Ala Thr Phe Gln Asn Thr Gly
 65 70 75 80

Thr Tyr Arg Cys Thr Glu Pro Gly Asp Pro Leu Gly Gly Ser Ala Ala
 85 90 95

Ile His Leu Tyr Val Lys Asp Pro Ala Arg Pro Trp Asn Val Leu Ala
 100 105 110

Gln Glu Val Val Val Phe Glu Asp Gln Asp Ala Leu Leu Pro Cys Leu
 115 120 125

Leu Thr Asp Pro Val Leu Glu Ala Gly Val Ser Leu Val Arg Val Arg
 130 135 140

Gly Arg Pro Leu Met Arg His Thr Asn Tyr Ser Phe Ser Pro Trp His
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Gly Phe Thr Ile His Arg Ala Lys Phe Ile Gln Ser Gln Asp Tyr Gln
 165 170 175

Cys Ser Ala Leu Met Gly Gly Arg Lys Val Met Ser Ile Ser Ile Arg
 180 185 190

Leu Lys Val Gln Lys Val Ile Pro Gly Pro Pro Ala Leu Thr Leu Val
 195 200 205

Pro Ala Glu Leu Val Arg Ile Arg Gly Glu Ala Ala Gln Ile Val Cys
 210 215 220

Ser Ala Ser Ser Val Asp Val Asn Phe Asp Val Phe Leu Gln His Asn
 225 230 235 240

Asn Thr Lys Leu Ala Ile Pro Gln Gln Ser Asp Phe His Asn Asn Arg
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Tyr Gln Lys Val Leu Thr Leu Asn Leu Asp Gln Val Asp Phe Gln His
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Ala Gly Asn Tyr Ser Cys Val Ala Ser Asn Val Gln Gly Lys His Ser
 275 280 285

-308-

Thr Ser Met Phe Phe Arg Val Val Glu Ser Ala Tyr Leu Asn Leu Ser
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Ser Glu Gln Asn Leu Ile Gln Glu Val Thr Val Gly Glu Gly Leu Asn
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Leu Lys Val Met Val Glu Ala Tyr Pro Gly Leu Gln Gly Phe Asn Trp
 325 330 335

Thr Tyr Leu Gly Pro Phe Ser Asp His Gln Pro Glu Pro Lys Leu Ala
 340 345 350

Asn Ala Thr Thr Lys Asp Thr Tyr Arg His Thr Phe Thr Leu Ser Leu
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Gln Cys Ser Gly His Thr Asp Arg Cys Asp Glu Ala Gln Val Leu Gln
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Val Trp Asp Asp Pro Tyr Pro Glu Val Leu Ser Gln Glu Pro Phe His
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Lys Val Thr Val Gln Ser Leu Leu Thr Val Glu Thr Leu Glu His Asn
 465 470 475 480

Gln Thr Tyr Glu Cys Arg Ala His Asn Ser Val Gly Ser Gly Ser Trp
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Ala Phe Ile Pro Ile Ser Ala Gly Ala His Thr His Pro Pro Asp Glu
 500 505 510

Phe Leu Phe Thr Pro Val Val Val Ala Cys Met Ser Ile Met Ala Leu

- 309 -

515		520		525
Leu 530	Leu 530	Leu 535	Tyr 540	Lys 540
Lys 545	Tyr 545	Gln 550	Val 550	Arg 550
Tyr 565	Thr 565	Phe 570	Ile 570	Asp 575
Phe 580	Pro 580	Arg 585	Asn 585	Leu 590
Phe 595	Gly 595	Lys 600	Val 605	Val 605
Ala 610	Val 610	Lys 615	Met 620	Leu 620
Asp 625	Glu 625	Lys 630	Glu 635	Ile 640
Gly 645	Gln 645	His 650	Val 655	Asn 655
Gly 660	Pro 660	Val 665	Ile 670	Thr 670
Asn 675	Phe 675	Leu 680	Arg 685	Arg 685
Pro 690	Gly 690	Gln 695	Asp 700	Pro 700
Glu 705	Lys 705	Lys 710	Tyr 715	Val 720
Asp 725	Thr 725	Tyr 730	Val 735	Met 735
Phe 740	Ser 740	Glu 745	Gln 750	Asp 750

-310-

Arg Asp Leu Leu His Phe Ser Ser Gln Val Ala Gln Gly Met Ala Phe
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Leu Ala Ser Lys Asn Cys Ile His Arg Asp Val Ala Ala Arg Asn Val
 770 775 780

Leu Leu Thr Asn Gly His Val Ala Lys Ile Gly Asp Phe Gly Leu Ala
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Leu Pro Val Lys Trp Met Ala Pro Glu Ser Ile Phe Asp Cys Val Tyr
 820 825 830

Thr Val Gln Ser Asp Val Trp Ser Tyr Gly Ile Leu Leu Trp Glu Ile
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Phe Tyr Lys Leu Val Lys Asp Gly Tyr Gln Met Ala Gln Pro Ala Phe
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Ala Pro Lys Asn Ile Tyr Ser Ile Met Gln Ala Cys Trp Ala Leu Glu
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Pro Thr His Arg Pro Thr Phe Gln Gln Ile Cys Ser Phe Leu Gln Glu
 900 905 910

Gln Ala Gln Glu Asp Arg Arg Glu Arg Asp Tyr Thr Asn Leu Pro Ser
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Ser Ser Arg Ser Gly Gly Ser Gly Ser Ser Ser Ser Glu Leu Glu Glu
 930 935 940

Glu Ser Ser Ser Glu His Leu Thr Cys Cys Glu Gln Gly Asp Ile Ala
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<211> 397

<212> PRT

<213> Homo sapiens

<400> 146

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Ile Ile Gly Ser Phe Asn Gly Ala Leu Ala Ala Val Pro Val Gln Asp
 20 25 30

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 35 40 45

Pro Glu Asp Val Ser Glu Val Ile Phe Gly His Val Leu Ala Ala Gly
 50 55 60

Cys Gly Gln Asn Pro Val Arg Gln Ala Ser Val Gly Ala Gly Ile Pro
 65 70 75 80

Tyr Ser Val Pro Ala Trp Ser Cys Gln Met Ile Cys Gly Ser Gly Leu
 85 90 95

Lys Ala Val Cys Leu Ala Val Gln Ser Ile Gly Ile Gly Asp Ser Ser
 100 105 110

Ile Val Val Ala Gly Gly Met Glu Asn Met Ser Lys Ala Pro His Leu
 115 120 125

Ala Tyr Leu Arg Thr Gly Val Lys Ile Gly Glu Met Pro Leu Thr Asp
 130 135 140

Ser Ile Leu Cys Asp Gly Leu Thr Asp Ala Phe His Asn Cys His Met
 145 150 155 160

Gly Ile Thr Ala Glu Asn Val Ala Thr Lys Trp Gln Val Ser Arg Glu
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Asp Gln Asp Lys Val Ala Val Leu Ser Gln Asn Arg Thr Glu Asn Ala
 180 185 190

Gln Lys Ala Gly His Phe Asp Lys Glu Ile Val Pro Val Leu Val Ser

- 312 -

195	200	205
Thr Arg Lys Gly Leu Ile Glu Val Lys Thr Asp Glu Phe Pro Arg His 210 215 220		
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Gly Ala Ala Ala Val Ala Leu Met Lys Lys Ser Glu Ala Asp Lys Arg 260 265 270		
Gly Leu Thr Pro Leu Ala Arg Ile Val Ser Trp Ser Gln Val Gly Val 275 280 285		
Glu Pro Ser Ile Met Gly Ile Gly Pro Ile Pro Ala Ile Lys Gln Ala 290 295 300		
Val Thr Lys Ala Gly Trp Ser Leu Glu Asp Val Asp Ile Phe Glu Ile 305 310 315 320		
Asn Glu Ala Phe Ala Ala Val Ser Ala Ala Ile Val Lys Glu Leu Gly 325 330 335		
Leu Asn Pro Glu Lys Val Asn Ile Glu Gly Gly Ala Ile Ala Leu Gly 340 345 350		
His Pro Leu Gly Ala Ser Gly Cys Arg Ile Leu Val Thr Leu Leu His 355 360 365		
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<210> 147

<211> 390

<212> PRT

<213> Homo sapiens

- 313 -

<400> 147

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 20 25 30

Val Thr Ile Lys Cys Pro Leu Pro Glu Met His Val Arg Ile Tyr Leu
 35 40 45

Cys Arg Glu Met Ala Gly Ser Gly Thr Cys Gly Thr Val Val Ser Thr
 50 55 60

Thr Asn Phe Ile Lys Ala Glu Tyr Lys Gly Arg Val Thr Leu Lys Gln
 65 70 75 80

Tyr Pro Arg Lys Asn Leu Phe Leu Val Glu Val Thr Gln Leu Thr Glu
 85 90 95

Ser Asp Ser Gly Val Tyr Ala Cys Gly Ala Gly Met Asn Thr Asp Arg
 100 105 110

Gly Lys Thr Gln Lys Val Thr Leu Asn Val His Ser Glu Tyr Glu Pro
 115 120 125

Ser Trp Glu Glu Gln Pro Met Pro Glu Thr Pro Lys Trp Phe His Leu
 130 135 140

Pro Tyr Leu Phe Gln Met Pro Ala Tyr Ala Ser Ser Ser Lys Phe Val
 145 150 155 160

Thr Arg Val Thr Thr Pro Ala Gln Arg Gly Lys Val Pro Pro Val His
 165 170 175

His Ser Ser Pro Thr Thr Gln Ile Thr His Arg Pro Arg Val Ser Arg
 180 185 190

Ala Ser Ser Val Ala Gly Asp Lys Pro Arg Thr Phe Leu Pro Ser Thr
 195 200 205

Thr Ala Ser Lys Ile Ser Ala Leu Glu Gly Leu Leu Lys Pro Gln Thr
 210 215 220

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Pro Ser Tyr Asn His His Thr Arg Leu His Arg Gln Arg Ala Leu Asp
 225 230 235 240

Tyr Gly Ser Gln Ser Gly Arg Glu Gly Gln Gly Phe His Ile Leu Ile
 245 250 255

Pro Thr Ile Leu Gly Leu Phe Leu Leu Ala Leu Leu Gly Leu Val Val
 260 265 270

Lys Arg Ala Val Glu Arg Arg Lys Ala Leu Ser Arg Arg Ala Arg Arg
 275 280 285

Leu Ala Val Arg Met Arg Ala Leu Glu Ser Ser Gln Arg Pro Arg Gly
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Ser Pro Arg Pro Arg Ser Gln Asn Asn Ile Tyr Ser Ala Cys Pro Arg
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Arg Ala Arg Gly Ala Asp Ala Ala Gly Thr Gly Glu Ala Pro Val Pro
 325 330 335

Gly Pro Gly Ala Pro Leu Pro Pro Ala Pro Leu Gln Val Ser Glu Ser
 340 345 350

Pro Trp Leu His Ala Pro Ser Leu Lys Thr Ser Cys Glu Tyr Val Ser
 355 360 365

Leu Tyr His Gln Pro Ala Ala Met Met Glu Asp Ser Asp Ser Asp Asp
 370 375 380

Tyr Ile Asn Val Pro Ala
 385 390

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International Bureau



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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
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Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted
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CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK,
MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD,
SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ,
VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS,
MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent
(AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent
(AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB,
GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF,
BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN,
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0124145.4 8 October 2001 (08.10.2001) GB

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(74) Common Representative: BAYER HEALTHCARE
AG; 51368 Leverkusen (DE).

Published:

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG,

(88) Date of publication of the international search report:
12 February 2004

*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: GENES AND PROTEINS FOR PREVENTION, PREDICTION, PROGNOSIS AND THERAPY OF CARDIOVASCU-
LAR DISEASE

(57) Abstract: Genes that are differentially expressed in blood vessels of cardiovascular disease patients versus blood vessels of
normal people are disclosed. The genes provide novel methods, uses and compositions for the prediction, prevention, diagnosis,
prognosis and treatment of cardiovascular disease.

WO 2003/031650 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/11034

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 C07K14/47 C12N15/12 C12N15/11 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, SEQUENCE SEARCH, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01 72774 A (MIDGLEY CAROL ;CYCLACEL LTD (GB); DEAK PETER (GB); GLOVER DAVID MO) 4 October 2001 (2001-10-04) page 6, line 7-11 page 41, line 14-18 ---	1-3, 5-11,13
X	US 6 087 117 A (STEEG PATRICIA SCHRIVER ET AL) 11 July 2000 (2000-07-11) the whole document ---	5,6,13
A	BARRANS ET AL.: "Construction of a human cardiovascular cDNA microarray: portrait of the failing heart" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 280, January 2001 (2001-01), pages 964-969, XP002248512 the whole document --- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"B" document member of the same patent family

Date of the actual completion of the international search

22 July 2003

Date of mailing of the international search report

12.11.2003

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bort, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 02/11034

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>MCCAFFREY ET AL.: "High-level of expression of Egr-1 and Egr-1-inducible genes in mouse and human atherosclerosis" THE JOURNAL OF CLINICAL INVESTIGATION, vol. 105, no. 5, March 2000 (2000-03), pages 653-662, XP002248513 abstract</p> <p>---</p>	
A	<p>LAWN ET AL.: "The Tangier disease gene product ABC1 controls the cellular apolipoprotein-mediated lipid removal pathway" THE JOURNAL OF CLINICAL INVESTIGATION, vol. 104, no. 8, October 1999 (1999-10), pages R25R-R31, XP002248514 abstract</p> <p>-----</p>	

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/11034

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 1-3 (partially), 14
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☒ Claims Nos.: 4, 12
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-3, 5-11, 13 all partially

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Claims Nos.: 1-3 (partially), 14

Claims 1-3 are directed to a diagnostic method practised on the human/animal body. According to Rule 39.1(iv) PCT, subject-matter regarding methods for treatment of the human/animal body is not required to be searched. Notwithstanding the mentioned objection, the search has been carried out and based on the alleged effects of the sequences claimed.

Claim 14 refers a computer readable medium, which are merely physical entities for the presentation of information. According to Rule 39.1(v) PCT subject-matter regarding presentation of information is not required to be searched. Therefore, claim 14 has not been searched.

Continuation of Box I.2

Claims Nos.: 4, 12

Claim 4 refers to a diagnostic kit defined by reference to a desirable characteristic or property, namely a diagnostic kit for conducting the method of any of claims 1-3. The claim covers all diagnostic kits having this property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT therefor. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independently of the above reasoning, the claim also lacks clarity (Article 6 PCT). An attempt is made to define the reagent by reference to a result to be achieved. Again, this lack of clarity in the present case renders a meaningful search over the whole claimed scope impossible. Moreover, the search could not even been carried out for those parts of the claim which would appear clear, supported and disclosed, namely the examples, since the present application does not provide examples.

Claim 12 refers to a reagent defined by reference to a desirable characteristic or property, namely a reagent that regulates the activity of the polynucleotides listed in said claim. The claim covers all reagents having this property, whereas the application does not provide support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT therefor. In the present case, the claim so lacks support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independently of the above reasoning, the claim also lacks clarity (Article 6 PCT). An attempt is made to define the reagent by reference to a result to be achieved. Again, this lack of clarity in the present case renders a meaningful search over the whole claimed scope impossible. Moreover, the search could not even been carried out for those parts of the claim which would appear clear, supported and disclosed, namely the examples, since

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

the present application does not provide examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-3, 5-11, 13 (all partially)

Invention 1

(Pharmaceutical) Composition and array comprising a polynucleotide (or derivatives) comprising SEQ ID No. 1; methods using them; and use of the polynucleotide (or derivatives) for the preparation of compositions

2. Claims: 1-3, 5-11, 13 (all partially)

Invention 2

(Pharmaceutical) Composition and array comprising a polynucleotide (or derivatives) comprising SEQ ID No. 2; methods using them; and use of the polynucleotide (or derivatives) for the preparation of compositions

Inventions 3-74

Ibidem for SEQ ID Nos. 3-74

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/11034

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0172774	A	04-10-2001	AU 3943401 A	08-10-2001
			EP 1330472 A2	30-07-2003
			WO 0172774 A2	04-10-2001
			US 2003152945 A1	14-08-2003

US 6087117	A	11-07-2000	US 6423836 B1	23-07-2002
			US 6329198 B1	11-12-2001
			AT 206129 T	15-10-2001
			AU 643971 B2	02-12-1993
			AU 7042491 A	16-05-1991
			CA 2067797 A1	19-04-1991
			DE 69033810 D1	31-10-2001
			DE 69033810 T2	28-03-2002
			DK 495910 T3	14-01-2002
			EP 0495910 A1	29-07-1992
			ES 2164634 T3	01-03-2002
			JP 3295358 B2	24-06-2002
			JP 10212299 A	11-08-1998
			JP 2758500 B2	28-05-1998
			JP 4506457 T	12-11-1992
			WO 9105793 A1	02-05-1991
			US 5753437 A	19-05-1998

Form PCT/SA/210 (patent family annex) (July 1992)